Exhibit C

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Via Email and Federal Express May 9, 2016

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Food and Drug Administration
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Re: Liver Injury Controversy Regarding OxyElite Pro

Dear Mr. Correll:

This letter is in response to the agency's letter from January 15, 2014 (Appendix 1),[1] in which the agency informed USPlabs that FDA was designating the recall of aegeline-containing OxyElite Pro as a Class I recall on the basis of evidence that this product was associated with liver injury. We have also received notice from the Dallas District Office that FDA considers the recall completed.[2] In the interim, we have been investigating the allegations that gave rise to the recall and write now with what we believe to be new and material information concerning the allegations that aegeline-containing OxyElite Pro caused liver injury.

In summary, information we have received refutes the conclusion that OxyElite Pro caused these injuries. The patients' medical records, which USPlabs obtained in the course of civil litigation, show that, before they developed liver injury, the patients in Hawaii Queen's Medical Center ("QMC") were sicker than initially thought, and the records contain evidence of alternative etiologies to explain the patients' liver illnesses. For example, most of the Hawaii patient records showed evidence of viral infection, pain medication overuse, and/or illegal drug use. Nearly all of the patients used many different drugs and/or dietary supplements around the time of onset of their liver illnesses. These records do not support statements made by the QMC, nor assertions by the Hawaii Department of Health (Hawaii DOH), the Centers for Disease Control and Prevention (CDC), and the Federal Food and Drug Association (FDA)

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[1] The letter was from then-director of the Office of Compliance, Jennifer A. Thomas. Letter from J. Thomas, FDA, to J. Geissler (Jan. 15, 2014). All the references in our present letter, including the 2014 letter from Jennifer A. Thomas, will be included on a CD sent to William Correll along with a hard copy of this letter.

[2] Letter from C. Hamblin, FDA, to A. Rodriguez (Oct. 21, 2015).

(collectively the "regulators"), that the patients at QMC were "previously healthy" and used no drugs or other products that could have caused their liver disease.[3]

We also question the QMC doctors' use of the Council for International Organizations of Medical Sciences's Roussel Uclaf Causality Assessment Method ("RUCAM") to report causality scores.[4] As discussed below (in Section III.D), the QMC doctors admitted under oath in depositions that they had rescored, and ultimately increased, their patients' RUCAM scores by one point, because they expected the scores to be higher, which would support their conclusion that OxyElite Pro was dangerous.[5]

The facts presented below are from original documentation that we have obtained through private litigation and under public records laws. We summarized the key details from the medical records of some of the case patients in a May 6, 2015 letter to CDC, the Hawaii DOH, and FDA (Appendix 1).[6] (Our discussion below refers to the same patient numbering system used by the QMC doctors as well as in our May letter.) Since then, ongoing lawsuits against USPlabs by many of the Hawaii case patients have provided us with thousands of documents that relate directly to this matter. These documents include the medical records of

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[3] *E.g.*, Sarah Y. Park et al., "Acute Hepatitis and Liver Failure Following the Use of a Dietary Supplement Intended for Weight Loss or Muscle Building — May-October 2013," 62 *Morbidity and Mortality Weekly Report* 817 (Oct. 11, 2013) (article authored by the Hawaii DOH and CDC), *available at* http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6240a1.htm; FDA Consumer Updates, "OxyElite Pro Supplements Recalled" (Nov. 2013), *available at* http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM375497.pdf.

[4] This method is also sometimes known as "CIOMS."

[5] Roytman Deposition, at 156:14-158:1 (asked why she upgraded all her RUCAM values right before publication, Dr. Roytman explained that it was to match her expectations: "I reviewed the -- the reason that I went looking for it is that I was re-reading the RUCAM criteria for -- yet one more time before sending the article for publication. And what always puzzled me and puzzled me at that time is that the scoring system that we reached in the original paper said 'possible, possible, probable' which didn't make sense to me with a clinical criteria. Like, it was quite probable in my mind. So I thought I would go one more time and double check the scoring system to convince myself that, you know, those patients who were, in my mind, were clearly fitting their criteria of at least "probable" injury were in the "possible" category. So I went back and I re-reviewed the article -- I mean the scoring system." "Q. So in -- based on your clinical work with these patients, you felt that several of them should have been higher, so you went back and rescored them, and they were then higher?" "That's right.").

[6] Letter from P. Hutt to Sarah Y. Park and others at the Hawaii DOH and CDC (May 6, 2015).

the liver patients treated at QMC; emails between the doctors at QMC;[7] and deposition testimony from Naoky Tsai, M.D., Marina Roytman, M.D., and Linda Wong, M.D.[8]

We compared these documents with the public documents related to the Hawaii patients that we received in 2014 from the Hawaii DOH under their freedom-of-information statute,[9] including the Hawaii DOH's correspondence with CDC and FDA, as well as with the QMC doctors. Copies of the documents cited in this current letter are included on a CD that is accompanying the physical copy of the letter for Mr. Correll, and we would be happy to provide a copy of this CD to anyone else who requests it.

I. INTRODUCTION TO TABLE 1: ATTACHED MEDICAL DETAILS ABOUT THE QMC PATIENTS

Table 1, attached to this letter, contains important details about the first eight Hawaii patients (Patients 1-8 from the QMC's 2014 publication[10]). These eight include the only three Hawaii patients that had acute liver failure -- the two transplants and one death case. These three patients are discussed in detail at the end of this letter. The medical facts in Table 1 have been made public previously in the civil lawsuits referenced above. Many of these facts also appear in three peer-reviewed publications[11] by Professor Rolf Teschke and his colleagues.

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[7] In 2015 we received two sets of documents from the QMC that we reference throughout this letter. We reference one in these footnotes with the designation "QC." We reference the other, which was withheld from us until November 2015, with the designation "WONG."

[8] Dr. Naoky Tsai is a gastroenterologist and hepatologist, and the head of the Queen's Liver Center. In 2013, he was the supervisor of Dr. Marina Roytman, who had not yet passed her medical boards. Dr. Roytman did not have any special expertise or training in liver illnesses, except what she learned from Dr. Tsai. Dr. Linda Wong is a transplant surgeon associated with the Queen's Liver Center.

[9] Letter to Gary Gill, Interim Director, Hawaii Department of Health (Jan. 14, 2014) (DOH 01037-01038) (requesting information under Uniform Information Practices Act, Hawaii Rev. Stat. ch. 92F); *see also* Document Receipt Pickup for Information Request from Jan. 14, 2014 (Sept. 2, 2014) (DOH 00001).

[10] M. Roytman et al., "Outbreak of Severe Hepatitis Linked to Weight-Loss Supplement OxyELITE Pro," 109 *Am. J. Gastroenterology* 1296 (Aug. 2014).

[11] R. Teschke & A. Eickhoff, "The Honolulu Liver Disease Cluster at the Medical Center: Its Mysteries and Challenges," 17 *Int. J. Mol. Sci.* 476 (2016); R. Teschke, A. Schwarzenboeck, C. Frenzel, J. Schulze, A. Eickhoff & A. Wolff, "The mystery of the Hawaii liver disease cluster in summer 2013: A pragmatic and clinical approach to solve the problem," 15 *Ann. Hepatol.* 91 (2016); R. Teschke, J. Schulze, A. Eickhoff, A. Wolff & C. Frenzel, "Mysterious Hawaii liver disease case – Naproxen overdose as cause rather than OxyELITE Pro?" 2 *J. Liver Clin. Res.* 1013 (2015).

These articles criticize the actions of the QMC doctors as lacking scientific justification and demonstrated that causality between OxyElite Pro and liver disease could not be established for any patient.

II. PROBLEMS WITH THE QMC INVESTIGATION OF THE CAUSES OF THE LIVER INJURIES -- AUGUST-OCTOBER 11, 2013

A. The QMC Doctors Based Their Medical Judgment on Incorrect Information from a Law Firm Website.

The OxyElite Pro/aegeline controversy began in late summer 2013 with doctors at the QMC in Honolulu, Hawaii. During August 2013, the QMC doctors noticed that a few of their liver patients reported taking OxyElite Pro, among other dietary supplements, over-the-counter (OTC) drugs, and prescription drugs. On August 15, 2013, a patient's spouse referred Dr. Marina Roytman of QMC to the website for Schmidt & Clark, a plaintiffs' law firm in Washington D.C. The patient's spouse said that the firm's website concerned "OxyElite Pro and the extremely toxic ingredient DMAA."[12] On August 28, 2013, Dr. Roytman forwarded the spouse's email to Dr. Wong, another QMC doctor.[13] Written to recruit clients, the firm's website stated[14] (without scientific justification) that DMAA-containing OxyElite Pro was associated with liver damage.[15] After reviewing the website, the QMC doctors began to ask their liver patients whether they took OxyElite Pro.

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[12] A spouse of a case patient sent an email to Dr. Roytman with a link to a law firm about DMAA litigation: "On behalf of my wife [] here is the link I was talking about concerning OxyElite Pro and the extremely toxic ingredient DMAA. I hope it can help." Email to Dr. Roytman (Aug. 15, 2013) (QC 2284).

[13] Email from Dr. Roytman to Dr. Wong entitled "Fwd: OxyElite Pro Link" (Aug. 28, 2013) (WONG 00003).

[14] This referenced website, www.schmidtandclark.com/oxyelite-pro, states that DMAA-containing OxyElite Pro causes liver damage or liver failure: "Serious side effects currently linked to OxyElite Pro include . . . liver failure."; "The most serious side effects reported in OxyElite Pro users include: . . . Liver damage or liver failure." This website has contained these claims since 2012.

[15] FDA had raise concerns that DMAA might cause heart problems, not liver damage, and this was later determined by the Department of Defense to be unlikely. DOD, "Report of the Department of Defense 1,3 Dimethylamylamine (DMAA) Safety Review Panel" (June 3, 2013), *available at* http://home.fhpr.osd.mil/Libraries/pdf/Report_of_the_DoD_DMAA_Safety_Review_Panel_2013.sflb.ashx.

By the first week of September 2013, as a result of repeated questioning of their liver patients (including re-questioning of patients who initially denied OxyElite Pro use[16]), the QMC doctors identified five patients who reported consumption of OxyElite Pro before their liver illnesses.

Based apparently on their review of the April 24, 2012 FDA warning letter on DMAA[17] and the law firm's website, the QMC doctors concluded that their patients' illnesses were caused by DMAA. A pathology report by Dr. Peter Bryant-Greenwood of the QMC dated August 17, 2013, stated that one of the liver biopsies was "consistent with the patient's history of DMAA supplement use."[18] It is unclear how Dr. Greenwood came to this conclusion when there is no scientific or medical literature stating that DMAA causes liver disease and the patient had not consumed a DMAA dietary supplement. The QMC doctors proceeded to discuss "how to tie the pathology into the results, particular [sic] if they give us a 'common pattern of liver injury' which would tie these cases together, in addition to their use of OxyElite Pro."[19]

B. A QMC Doctor Alerted the Media Without Having Appropriate Data to Link OxyElite Pro and Liver Disease.

One of the QMC doctors, Dr. Linda Wong, a transplant surgeon, went to the media with a story about OxyElite Pro before any data analysis had been done.[20] On September 3, 2013, she saw the patient who would become Patient 1 in the QMC doctors' publications. She determined that Patient 1's condition was possibly attributable to DMAA and OxyElite Pro.[21] She did not know the actual ingredients in OxyElite Pro and did not research or investigate the subject.[22] Dr. Wong did not undertake any investigation or testing of Oxy Elite Pro, did not

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[16] One of the first patients, "Initially denied dietary supplements, but later confirmed." Email from Curtis Toma to Dr. Sarah Park (Sept. 19, 2013) (DOH 03101-03103).

[17] On April 24, 2012, FDA sent 11 warning letters to manufacturers and distributors of dietary supplements containing DMAA. USPlabs was one of the 11 companies. *See* FDA, DMAA in Dietary Supplements (July 16, 2013), http://www.fda.gov/Food/DietarySupplements/ProductsIngredients/ucm346576.htm.

[18] Pathology Report for Patient 3 (Aug. 17, 2013) (QC 898-899); *see also* Email from Curtis Toma to Dr. Sarah Park (Sept. 19, 2013) (DOH 03101-03103) (reporting a liver biopsy as "consistent with DMAA induced damage").

[19] Email from Poerzgen to Dr. Wong, Dr. Roytman and others (Sept. 13, 2013) (QC 2315).

[20] D. Thompson, "The Transplant Surgeon Who Went Out On A Limb," *Honolulu Magazine* (June 2014) ("On the night of Sept. 3, 2013, Wong . . . phoned her hospital's chief and told him the public needed to be warned about OxyElite Pro. The chief listened with interest, but cautioned her about jumping to conclusions. He suggested she write a scientific paper.")

[21] Wong Deposition, at 109:13-19

[22] *Id.*, at 110:4-7.

attempt to contact the company, and did not review existing scientific or medical literature regarding the ingredients in OEP.[23] She took photos of the product at GNC to provide to reporters and called Queen's Medical Center CEO, Art Ushijima concerning her plans to go to the media. Mr. Ushijima cautioned her against leaping to any conclusions and urged her to wait until the QMC had analyzed the patients' data before alarming the public.[24]

Without heeding this advice, on September 4, 2013 Dr. Wong contacted the *Honolulu Star Advertiser*, the largest daily newspaper in Hawaii. In an email to Dr. Roytman, she explained her decision to go to the media and criticized the QMC for waiting "until they are part of the flock rather than taking the chance to lead the way."[25]

On September 5, 2013, the *Honolulu Star Advertiser* ran the first media story about the Hawaii patients.[26] Quoting Dr. Wong, it reported that at least five patients "developed acute liver failure in the past month after taking a weight-loss supplement deemed unsafe by U.S. Food and Drug Administration."[27] The article focused on DMAA. At that time, Dr. Wong did not know that OxyElite Pro with DMAA was no longer being manufactured or that alternative versions without DMAA were being marketed. Dr. Wong was quoted in the article as stating that OxyElite Pro had been banned, which was not true.

In the first two weeks after that first article, an email from Dr. Wong to Dr. Roytman indicated that she was frustrated that the article about OxyElite Pro had not caused sufficient "drama."[28] The original article appeared on page B-5 of the business section, and Dr. Wong was disappointed that it was not more prominently featured. She worried that media interviews with "people outside of gyms, vitamin shops" would not "be enough drama."[29] By September 23, 2013, Dr. Wong asked her QMC colleagues for ideas about the best way to "sell the story" about OxyElite Pro to the press.[30] It would be best, she stated, to have "a patient tell their plight," preferably a transplant patient who could "sell the story,"[31] and she explained that she

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[23] *Id.* at 112:5-7.

[24] *Id.* at 110:8-11; *see also* email from Dr. Wong to Dr. Roytman (Sept. 4, 2013) (QC 2289) (summarizing Dr. Wong's conversation with her supervisor).

[25] Email from Dr. Wong to Dr. Roytman (Sept. 4, 2013) (QC 2289).

[26] Kristen Consillio, "Weight-loss pills may damage liver: doctor" *Honolulu Star-Advertiser* (Sept. 5, 2013).

[27] *Id.*

[28] Email from Dr. Wong to Dr. Roytman and others (Sept. 23, 2013) (QC 2404).

[29] *Id.*

[30] *Id.*

[31] *Id.*

was trying to get a transplant patient to "warm up to the idea."[32] Dr. Wong concluded her September 23, 2013 email as follows: "This is kinda complicated.....not the usual way in which I manipulate the media."[33]

C. The QMC Doctors Claim to Manipulate the Regulators Regarding OxyElite Pro.

In mid-September 2013, Dr. Wong brought the story to the Hawaii Department of Health ("DOH") in what the documents indicate was an attempt to raise the public profile of the story.[34] On September 23, 2013, Dr. Wong spoke with Dr. Sarah Park, State Epidemiologist at the Hawaii DOH. The next day Dr. Roytman sent information about the case patients to Dr. Park and the Hawaii DOH.[35] Dr. Park immediately launched an investigation.[36] By then, the QMC doctors had found seven liver-injury patients that they claimed took OxyElite Pro.

The QMC doctors were pleased to have caught the attention of the Hawaii DOH and compared themselves to superheroes. Dr. Roytman wrote to Dr. Wong on the night of September 24, 2013: "Great idea to contact Dr. Park. She immediately jumped on it and launched an investigation. Totally awesome."[37] Dr. Wong responded: "I know how to make drama. This is the cleanest way to do it."[38] Dr. Wong explained that it was difficult for the QMC doctors to control what patients and other staff might say or do, and lawyers could come after the QMC doctors "from both sides" for what they were doing. Dr. Wong continued "It's tough to save the planet here. Superman didn't have all these challenges."[39] Dr. Roytman responded they should change their "slogan" to match their role as superheroes: "saving the planet: one liver at a time:)"[40] Again, the emails indicate that Dr. Wong and her colleagues were considerably more concerned with raising the public profile of the issue than with finding additional support for their claims about DMAA:

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[32] *Id.*

[33] *Id.*

[34] Email from Dr. Wong to Dr. Roytman (Sept. 24, 2013) (QC 2414) ("If DOH gets involved, they can say anything they want to the media or anyone and not get in trouble. They're the answer key. They can get our message out there without us getting attacked by lawyers and without my going to the crazy hoops and red tape that QMC has.").

[35] Email from Dr. Roytman to Sarah Park (Sept. 24, 2013) (DOH 1297).

[36] Email from Dr. Roytman to Dr. Wong (Sept. 24, 2013) (QC 2415).

[37] *Id.*

[38] Email from Dr. Wong to Dr. Roytman (Sept. 24, 2013) (QC 2414).

[39] *Id.*

[40] *Id.*

> I knew I could find a way to do this. I just had to think hard enough. There's always a way. If DOH gets involved, they can say anything they want to the media or anyone and not get in trouble. They're the answer key. They can get our message out there without us getting attacked by lawyers and without my going to the crazy hoops and red tape that QMC has.[41]

One day later, September 25, 2013, the Hawaii DOH sent the first medical alert about the Hawaii patients, soliciting additional cases from Hawaii health care professionals.[42] Dr. Wong wrote to Dr. Roytman: "I will have to remember Sarah Park.....she knows how to get stuff done! (this is pretty much how I roll.....figure out who in the environment I can manipulate to move mountains....)."[43]

These early actions by the QMC doctors and the increasing media presence irreparably biased the public and made it difficult for regulators to investigate what were largely unsupported allegations. By September 25, 2013, the Hawaii DOH was communicating with CDC and FDA. However, at the outset, several factors made the investigation difficult. First, because the federal government was about to shut down on October 1, 2013, with many federal workers unable to work, federal regulators needed to rely heavily on the Hawaii DOH and the reports of the QMC doctors. Second, regulators were already concerned with "bias" in the early investigation. The media had already exploded with articles and television reports about OxyElite Pro. The news outlets that reported on the Hawaii DOH alert from September 25 uniformly named OxyElite Pro, which Dr. Park herself had cautioned against because it "potentially could draw attention away from what may instead be the true etiologic agent."[44] Dr. Park was even interviewed for a September 26 story that named OxyElite Pro on the local news.[45] At the outset, therefore, CDC questioned the bias early in the investigation given the source of the information regarding the case patients was from a transplant surgeon (Dr. Wong) and the information was perhaps "skewed."[46]

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[41] *Id.*

[42] Hawaii DOH Medical Advisory, "Acute Hepatitis and Liver Failure Potentially Associated with Ingestion of Dietary Supplements" (Sept. 25, 2013) (DOH 00425-00426).

[43] Email from Dr. Wong to Dr. Roytman (Sept. 26, 2013) (QC 2417).

[44] Email from Sarah Park to Loretta J. Fuddy (Sept. 25, 2013) (DOH 02389).

[45] Lynn Kawano, "More cases of liver failure linked to diet supplement," *Hawaii News Now* (Sept. 26, 2013, updated Oct. 3, 2013), http://www.hawaiinewsnow.com/story/23544063/weight-loss-supplement-linked-to-liver-failure.

[46] Email from Lauren Lewis to Sarah Park and Melissa Viray (Sept. 25, 2013) (DOH 02445) ("Perhaps the cases we know about are skewed because of how they were identified (an organ transplant specialist).")

This situation was exacerbated by the fact that the physicians at QMC continued to promote Oxy Elite Pro as a "serious public health threat," and requested that they "spread this information" among all of the residents.[47] When asked about the specific products involved, for example,[48] Dr. Roytman responded with a broad and sweeping statement: "OxyElite Pro is the culprit . . . all of our patients took it."[49]

On October 8, 2013, FDA, CDC, and the Hawaii DOH all issued public warnings about OxyElite Pro and the Hawaii liver cases, [50] and on October 11, 2013, the Hawaii DOH and CDC also published an abbreviated report on the Hawaii cases in the "Notes from the Field" section of CDC's *Morbidity and Mortality Weekly Report* (MMWR).[51] On October 11, 2013, FDA sent a warning letter to USPlabs about OxyElite Pro, claiming aegeline, a component of the Bael fruit (*Aegle marmelos*) consumed throughout the world, was a new dietary ingredient and was not present in the food supply in a form in which the food had not been chemically altered.[52]

In the midst of this activity, Hawaii officials began to understand the consequences of the media attention. Dr. Park stated:

> it does appear that despite our best efforts, the public is already biased (mostly by their clinicians) in thinking that OEP is the culprit as it's difficult to get them to identify other supplements they may be taking concurrently.[53]

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[47] Email from Dr. Roytman to various University of Hawaii Professors (Sept. 26, 2013) (QC 2426)

[48] Email from Elizabeth Tam to Dr. Roytman (Sept. 26, 2013) (QC 2426)

[49] Email from Dr. Roytman to Elizabeth Tam and various University of Hawaii Professors (Sept. 26, 2013) (QC 2426) ("OxyElite Pro is the culprit. It is not formally mentioned in the advisory as the investigation is still ongoing. However, all of our patients took it.")

[50] Park et al., *supra* note 3.

[51] FDA MedWatch, OxyElite Pro: Health Advisory—Acute Hepatitis Illness Cases Linked to Product Use (Oct. 8, 2013), *available at* http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm370857.htm; CDC Health Advisory: Acute Hepatitis and Liver Failure Following the Use of a Dietary Supplement Intended for Weight Loss or Muscle Building (Oct. 8, 2013) (DOH 00556-00557); Hawaii DOH, Medical Advisory UPDATE: Acute Hepatitis and Liver Failure Potentially Associated with Ingestion of Dietary Supplements (Oct. 8, 2013) (DOH 00429-00430).

[52] FDA Warning Letter to USPlabs LLC (Oct. 11, 2013).

[53] Email from Sarah Park to Lauran Lewis, CDC, and others (Oct. 1, 2013) (DOH 02532; 02534).

A colleague at the CDC agreed, explaining that the regulators had already introduced further bias into the investigation, because they began questioning patients by asking about use of OxyElite Pro, and only later asked about other drugs and dietary supplements.[54] CDC and the Hawaii DOH knew that the patient population used "multiple nutritional supplements" and that the media and physician bias would lead to the other dietary supplements being underreported.[55] In this climate it is also possible that patients may have had self-serving motives for citing use of Oxy Elite Pro, including the ability to be part of the resulting civil lawsuits. Adding to the media bias, several personal injury attorneys also began to solicit to consumers of OxyElite Pro. One law firm in particular, Wayne Parsons Law Offices located in Honolulu, ran numerous unauthorized television and newspaper advertisements citing the Hawaii DOH health alert linking OxyElite Pro to an "explosion of liver failures."[56]

Indeed, even the original proponent of the media inquiry, Dr. Wong expressed concern. She stated: "I'm not sure if this is going to increase because there are more cases, or because anyone who takes these drugs may be a bit freaked out. The hypochondriacs may start coming out soon ..."[57] In short, these circumstances made any information collected about the connection between OxyElite Pro and liver disease inherently unreliable.

III. ACTS AND STATEMENTS BY THE QMC DOCTORS THAT FURTHER OBSCURED THE CAUSES OF THEIR PATIENTS' LIVER ISSUES

A. The QMC Doctors Incorrectly Reported That Common Viral Causes of Hepatitis Were Ruled out for Their Hawaii Case Patients.

The QMC doctors did not properly investigate and exclude the most common viral causes of hepatitis before concluding that OxyElite Pro was the cause of liver damage. Although the QMC doctors stated that they had excluded other common causes of liver disease, the documents we have obtained, along with their deposition testimony, confirm that was not the case.

1. The Nine Key Viral Causes of Hepatitis (Hepatitis A-E, VZV, CMV, HSV, and EBV) Were Not Properly Ruled out for Any of the Patients.

Drug-induced liver injury (DILI) -- also called herb-induced liver injury (HILI) when the article is a dietary supplement -- is a diagnosis of exclusion. There is no test for it, and there is

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[54] Email from Ethel Taylor, CDC, to Melissa Viray, Hawaii DOH (Oct. 8, 2013) (DOH 02612).

[55] Email from Lauren Lewis, CDC, to Sarah Park and Melissa Viray (Sept. 27, 2013) (DOH 00061).

[56] Email from Loretta Fuddy to David Louie, Hawaii Attorney General and others (Oct. 5, 2013) (DOH 3526).

[57] Email from Dr. Wong to Sarah Park (Sept. 27, 2013) (DOH 01266).

no common signature of this illness. DILI and HILI can mimic other forms of liver damage.[58] Thus, viral causes must be excluded before making a HILI diagnosis. At a minimum, there are nine common viral causes of hepatitis that must be excluded in any potential HILI case: hepatitis A-E, varicella-zoster virus (VZV), cytomegalovirus (CMV), herpes simplex virus (HSV), and Epstein–Barr virus (EBV).

The QMC doctors should have been aware of this methodology. The case report form they used in their investigation of the Hawaii patients listed these nine key (and no other) viral causes.[59] The updated version of the causality assessment they used to assess their cases -- the Council for International Organizations of Medical Sciences's RUCAM system -- similarly lists these nine viruses as causing liver injury.[60] In cases of suspected herb-induced liver injury, experts recommend that investigators also exclude additional infectious causes (i.e., other viruses, as well as bacteria and protozoa).[61] The need to exclude less common infectious causes is also especially important for tropical locations like Hawaii or summertime illnesses like the ones seen at QMC in 2013. Unfortunately, the QMC doctors do not test for most of these alternative causes.

By their own records, and as they admitted in their depositions, the QMC doctors failed to test for or exclude many of these viruses. For example, the doctors failed to exclude hepatitis

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[58] Drug or herbal induced liver injury can mimic all forms of acute and chronic hepatobiliary diseases. In fact, "there are no reliable ways to separate drug-induced injury from liver diseases with other causes." *Drug-Induced Liver Disease*, 232 (Neil Kaplowitz & Laurie D. DeLeve eds., 3d Ed. 2013).

[59] The case report form (CRF) was completed for each of the QMC case patients. *E.g.*, CRF for Patient 1 (QC 851-852); CRF for Patient 2 (QC 871-872); CRF for Patient 3 (QC 894-895); CRF for Patient 4 (QC 901-902); CRF for Patient 5 (QC 923-924); CRF for Patient 6 (QC 940-941); CRF for Patient 7 (QC 947-948); CRF for Patient 8 (QC 955-956).

[60] *E.g.*, R. Teschke et al., "Herbal hepatotoxicity: challenges and pitfalls of causality assessment methods." 19 *World J Gastroenterol.* 2864 (2013). One of three articles cited by regulators in the MMWR report from October 8, 2013, Teschke (2013) explains the updated RUCAM scale in Table 5. *See also* R. Teschke et al., "Causality Assessment and Hepatotoxicity by Drugs and Dietary Supplements," 66 *Br. J. Clin. Pharmacol.* 758 (2008); R. Teschke et al., "Herbal hepatotoxicity: a tabular compilation of reported cases," 32 *Liver Int* 1543 (2012). The 2012 Teschke article, which refers to the updated causality assessment in the 2008 Teschke article, was cited by the QMC doctors in their Letter to the Editor about the cluster. Roytman et al., *supra* note 10. The author of the 1993 version of the RUCAM scale, Gaby Dana, has embraced the updates from Teschke (2013). G. Danan & R. Teschke, R., "RUCAM in Drug and Herb Induced Liver Injury: The Update," 17 *Int. J. Mol. Sci.* 14 (2016).

[61] *E.g.*, Teschke et al. (2008), *supra* note 60; Teschke et al. (2013), *supra* note 60. The QMC doctors did not investigate any other infectious causes, despite being in a tropical environment where other potential diseases should have been considered.

E in all of the patients they tested; to order the crucial HEV RNA test for any of the patients; and for the original eight patients, they failed to test for even HEV ab IgM for Patients 4-8.[62] Despite an offer from CDC to provide the tests, they also failed to test for HEV ab IgG in all of the patients.[63] Dr. Roytman admitted under oath that testing for hepatitis E by PCR analysis was not available at the QMC at the time.[64]

Both regulators and liver experts expressly advised QMC doctors to test for and exclude hepatitis E. On October 8, 2013, CDC advised QMC to test for hepatitis E,[65] offering itself to help with the tests.[66] CDC explained that hepatitis E cases are often mistakenly reported as cases of herb- or drug-induced liver injury and quoted a study of U.S. patients from the Drug-Induced Liver Injury Network (DILIN).[67] The QMC doctors received a similar message when the *New England Journal of Medicine* (*NEJM*) rejected their article as not fit for publication.[68] A NEJM reviewer noted that hepatitis E was not listed as one of the potential causes excluded in the treatment of the Hawaii patients. He explained to the QMC doctors that it must be excluded: "If HEV weren't excluded, authors must carry out HEV serology/PCR in the samples saved from these patients."[69] Even an employee within QMC noted the absence of hepatitis E testing.[70]

These shortcomings appear to be the reason that QMC's findings were rejected by peer-reviewed journals.[71] After receiving several rejections,[72] the QMC doctors finally published their

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[62] *See* Table 1 *infra* (summarizing results); QC 838; Expert Report of Robert G. Gish, M.D. (Sept. 22, 2015).

[63] Email from Chong-Gee Teo, CDC, to Dr. Tsai (Oct. 8, 2013) (QC 2561).

[64] Roytman Deposition, at 307:22-308:10.

[65] Email from Chong-Gee Teo, CDC, to Dr. Tsai (Oct. 8, 2013) (QC 2561).

[66] *Id.*

[67] *Id.* (citing T.J. Davern, et al., "Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury," 141 Gastorenterology 1665-72.e1-9 (2011)).

[68] Rejection Email from *New England Journal of Medicine* (Dec. 16, 2013) (QC 3156).

[69] *Id.* The reviewer explained: "This has been recommended by the latest Case Definition and Phenotye standardisation in DILI- Aithal GP et al., Clin Pharmacol Ther 2011; 89:806-15."

[70] Poerzgen asked: "What about HepE? Need to get from CRF" (undated) (QC 2263).

[71] Email from Dr. Wong to Dr. Roytman (Dec. 17, 2013) (QC 3161) (following rejection from the NEJM Dr. Wong recommends that they consider a lower tier GI journal "in which Naoky knows one of the editors reviewers.").

[72] In addition to the rejection by the *New England Journal of Medicine*, the paper that became the Roytman Letter was rejected by *Annals of Internal Medicine* on January 8, 2014 (QC 3148) and *JAMA* on January 28, 2014 (QC 3219). It was also originally rejected by the *American*

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eight key case patients, including the original seven highlighted repeatedly by regulators, as a Letter to the Editor ("Roytman Letter to the Editor") in the *American Journal of Gastroenterology* in August 2014.[73] Initially, the *American Journal of Gastroenterology* rejected the article. The journal only reconsidered the article when Dr. Roytman told them that *NEJM* had "invited" the regulators to submit a manuscript on the Hawaii cases.[74] Notably, the regulators' submission was not an invited manuscript, and *NEJM* rejected that paper as well.[75]

The QMC doctors also failed to test for others from among the nine common viruses. For example, they failed to test Patient 1 for CMV; Patient 4 for hepatitis B, hepatitis D, or VZV; Patient 5 for VZV; Patient 6 for VZV; and Patient 8 for VZV or HSV.[76]

The records show that many of the patients, including all seven original case patients, tested positive for some of the key viruses for which they did test. For example, Patient 1 tested positive for both anti-VZV and anti-EBV; Patient 2 was positive for anti-VZV; Patient 3 was positive for anti-VZV, CMV, and EBV; Patient 4 was positive for EBV, CMV, and HSV; Patient 5 was positive for EBV, CMV, and HSV; Patient 6 was positive for CMV; Patient 7 was positive for VZV, CMV, and EBV.[77] In nearly all cases, they failed to follow up on the titer changes for these viruses, which would have allowed them to track the course of active infections. See Table 1 (attached) for data about viral testing for all eight of the original patients.

The testing was, at best, disorganized and incomplete. Consequentially, many of the patients were likely not appropriately treated for these viruses with which they were infected, and the liver injuries were unjustifiably attributed to OxyElite Pro.

Journal of Gastroenterology on February 17, 2014 (QC 3231). The *American Journal of Gastroenterology* eventually reconsidered the paper and published it as a Letter to the Editor.

[73] Roytman et al., *supra* note 10.

[74] Email from Dr. Roytman to the *American Journal of Gastroenterology* (Feb. 25, 2014) (QC 3231) (urging the journal to reconsider their rejection, Dr. Roytman wrote: "We heard today from our collaborators at the Hawaii DOH that NEJM is considering publishing a paper that focuses on the epidemiological aspects of drug induced liver injury outbreak due to OxyElite Pro. It was an invited manuscript submission and a result of a collaborative effort between DOH, CDC and FDA.").

[75] Email from Park to Dr. Wong (Apr. 11, 2014) (WONG 00277) ("No, it wasn't invited, but they seemed very interested as they kept asking about it, and then they reject it but publish that editorial. :P").

[76] Table 1.

[77] *Id.*

2. The QMC Doctors Unjustifiably Told the Regulators, Scientists, and the Media That They Excluded Common Viral Causes of Hepatitis.

Despite evidence to the contrary, the QMC doctors made multiple statements to regulators, other scientists, and the media indicating that they had excluded common viral causes (and other common causes) of hepatitis. The following are some of the more prominent statements that the QMC doctors made in this respect:

- In October 2013, Naoky Tsai, Dr. Roytman's supervisor, told the CDC that alternative causes of hepatitis had been ruled out for all of their patients: "All cases were work [sic] up for viral A-E, autoimmune markers and Wilson disease. All were negative."[78]

- On October 8, 2013, in response to concern from CDC, Tsai stated that hepatitis E had been ruled out: "HEV is an exclusion criteria in our cases as defined by the AASLD guideline for ALF."[79] Trusting the QMC on their word, CDC responded: "Thanks, all. Looks like hep E doesn't contribute . . . ."[80]

- On November 4, 2013, QMC presented a poster of Patients 1-7 at an AASLD meeting. They forwarded the poster to the regulators. The poster stated: "Alternative causes (infectious, autoimmune, vascular and genetic) for acute hepatitis ruled out."[81]

- On January 27, 2014, the QMC doctors wrote in a statement to the Hawaii legislature: "Alternative causes of liver dysfunction have been systematically ruled out."[82]

These statements are inconsistent with the deposition testimony that the QMC doctors later gave regarding this matter, and show a failure to follow scientific methodology in reaching their conclusions.[83]

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[78] Email from Dr. Tsai as quoted in email from John Ward, CDC, to others at CDC (Oct. 24, 2013) (DOH 00262).

[79] Email from Dr. Tsai to Chong-Gee Teo, CDC (Oct. 8, 2013) (QC 2561).

[80] Email from Chong-Gee Teo to Dr. Tsai and others (Oct. 8, 2013) (QC 2561).

[81] M. Roytman et al., "Cluster of severe hepatotoxicity linked to the new formulation of OxyElite Pro" AASLD Poster (Nov. 4, 2013).

[82] QMC Doctors, Statement re S.B. 2067 (Jan. 27, 2014), http://www.capitol.hawaii.gov/Session2014/testimony/SB2067_Testimony_HTH_01-27-14_.pdf.

[83] The QMC doctors admitted under oath that they neither excluded hepatitis E nor followed the AASLD guidelines when investigating the case patients. Roytman Deposition, at 307:22-308:10; Tsai Deposition, at 151:22-24,152. The AASLD guidelines state that "viral hepatitis serologies" are "anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HEV, Anti-HCV, HCV RNA, HSV1 IgM, and VZV." William M. Lee et al., "AASLD Position Paper: The Management of Acute Liver

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3. Regulators Relied on the Problematic Information Provided by the QMC Doctors.

Federal and state regulators relied on the inconsistent statements from the QMC doctors in making their determinations. For example, the Hawaii DOH announced in a medical advisory:

> The Hawaii Department of Health (DOH) is investigating at least seven cases of severe acute hepatitis and fulminant liver failure. . . . These patients . . . have had negative findings for more common causes of acute hepatitis (e.g. infectious, autoimmune, metabolic) to date as well as negative findings for high risk social activities.[84]

The Hawaii DOH repeated this same assertion in the MMWR abbreviated report it co-authored with CDC on October 11, 2013. They wrote that all cases had:

> a negative evaluation for infections including viral hepatitis. Excluded were other etiologies such as pre-existing autoimmune hepatitis, chronic alcohol use, and chronic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, and hemochromatosis.[85]

Similar statements can be found in FDA's warning letter from October 11, 2013:

> There were no other consistent commonalities among the [Hawaii case patients given to FDA by the Hawaii DOH] other than exposure to Oxy Elite Pro. . . . And finally, rigorous clinical protocols were followed in the care of the patients to exclude and/or rule out known causes of liver disease (e.g., viral causes of hepatitis, autoimmune conditions, hemochromatosis, Wilson's disease, excess alcohol or acetaminophen ingestion, and alpha-1-antityrpsin deficiency). The absence of these causes of liver

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Failure: Update 2011, *available at* https://www.aasld.org/sites/default/files/guideline_documents/alfenhanced.pdf.

[84] Hawaii DOH, *Medical Advisory: Acute Hepatitis and Liver Failure Potentially Associated with Ingestion of Dietary Supplements* (Sept. 25, 2013) (DOH 00425-00426); *see also* Hawaii DOH, *Press Release: Department Of Health Investigates Hepatitis, Liver Failure in Persons Taking Dietary Supplements* (Sept. 26, 2013) ("Thus far, the cases have been negative for infectious causes, have no history of engaging in high-risk social activities, and have no identified commonly expected risk factors for liver failure.") (DOH 00493-94).

[85] Park et al., *supra* note 3.

> disease increases the likelihood that Oxy Elite Pro played a hepatotoxic role in these patients. Therefore, in the absence of a history of use or other evidence of safety establishing that aegeline is reasonably expected to be safe under the conditions recommended or suggested in the labeling . . . , your products are deemed to be adulterated . . . .[86]

In a recall letter it sent USPlabs on November 6, 2013, FDA repeated the problematic information from the QMC doctors about exclusion of alternative causes:

> Infectious causes that were ruled out after testing include: hepatitis A, B, C, and E; cytomegalovirus (CMV); Epstein Barr virus (EBV), herpes simplex virus (HSV), varicella-zoster virus (VZV), and *Leptospira*. Tests also ruled out the following non-infectious causes: auto-immune hepatitis, Wilson's disease, hemochromatosis, and alpha-1-antitrypsin deficiency. Alcoholic liver disease or acetaminophen ingestion was also ruled out.[87]

Regulators only recognized the need to consider infectious etiologies besides Hepatitis A-C on or about November 21, 2013, approximately two months after the investigation began. A CDC medical toxicologist emailed the Hawaii DOH's deputy state epidemiologist, asking: "Hey, do you think that we may be missing an infectious etiology? Those are outside my expertise . . . For example hepatitis E, or other bacterial pathogens (B. subtilis reported in Herbalife or B. cereus wich [sic] produces a toxin), mycoplasma, leptospirosis, typhus? Just covering all the bases."[88] The epidemiologist emailed back: "now I'm going to worry and think about it for the next three days."[89] Later that day she wrote: "Criminy, just looked up the B cereus toxin and liver failure thing. They totally didn't talk about THAT aspect during my boards review . . ."[90]

There does not appear to be evidence that regulators explored these plausible alternative etiologies beyond this short email exchange.

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[86] FDA Warning Letter to USPlabs LLC (Oct. 11, 2013).

[87] Letter from Michael R. Taylor to USPLabs LLC (Nov. 6, 2013).

[88] Email from Arthur Chang, CDC, to Melissa Viray, Hawaii DOH (Nov. 21, 2013) (DOH 05528).

[89] Email from Melissa Viray to Arthur Chang (Nov. 21, 2013) (DOH 05527).

[90] *Id*.

B. The Hawaii Patients Were Taking Extensive Lists of Prescription and OTC Drugs and Other Dietary Supplements.

1. The QMC Doctors Knew That Their Hawaii Patients Were Taking Many Drugs and Dietary Supplements Concurrent with OxyElite Pro.

According to their own records, the QMC doctor knew that patients consumed concomitant OTC and prescription drugs at the time of onset of their liver illnesses. For example, they knew that Patient 1 took Advair (fluticasone propionate and salmeterol) and Pro-Air (albuterol); Patient 2 took phentermine, Tylenol (acetaminophen), ibuprofen, and other unidentified migraine medicines; Patient 3 took acetaminophen (tested positive for acetaminophen when admitted to hospital with liver injury); Patient 4 took lisinopril; Patient 5 took acetaminophen (tested positive for acetaminophen when admitted to hospital with liver injury); Patient 6 took Alli (orlistat); Patient 7 took ibuprofen, lidocaine, and metoclopramide (toxicology results were positive for these drugs); and Patient 8 took Aleve (naproxen sodium), omeprazole, and Claritin (loratadine).[91] Acetaminophen and Orlistat are both known to cause severe liver toxicity,[92] but the QMC doctors did not disclose all of their patients' use of prescription and OTC drugs. In addition to aforementioned drugs, the patients' prescription records show that the patients were taking many other drugs at the time of onset of their liver illnesses. See Table 1 for data about the drugs and dietary supplements taken by the original eight patients.

Similarly, the QMC doctors knew that the patients were taking many other dietary supplements right before the onset of their liver illnesses. For example, Dr. Roytman's personal files show that Patient 1 took Amp Wheybolic 60; Patient 4 took Amberen, Garcinia cambogia, Super HD, CLK, Vita Chews, ProArgi-9, and HCA Supreme; Patient 5 took linoleic acid and GNC protein shake; and Patient 8 took GNC lean protein powder and Women's Active.[93]

The dietary supplement purchase records for these patients, which were obtained in the private litigation, were beyond what the QMC doctors recorded in their files. For example, we know that Patient 4 purchased 20 non-USPlabs dietary supplements in 2013 before her liver illness, as well as 13 after her illness.[94] She purchased similar numbers of dietary supplements in 2012 and 2014. Only three of these dietary supplements made it to the chart on the patients published in the Roytman Letter to the Editor,[95] although the documents indicate that the QMC

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[91] Case report forms for Patients 1-8, *supra* note 59; *see also* Table 1.

[92] *E.g.*, LiveTox Database. NIH. http://livertox.nih.gov/Acetaminophen.htm; http://livertox.nih.gov/Orlistat.htm.

[93] Case report forms for Patients 1-8, *supra* note 59; *see also* Table 1.

[94] Purchase records for Patient 4.

[95] Roytman et al., *supra* note 10.

doctors were aware of at least three more dietary supplements for this patient.[96] See Table 1 for details about dietary supplements used.

If the doctors suspected the true causes of their patients' conditions were ingestion of a drug or dietary supplement, the QMC doctors should have performed causality assessments with these many other drugs and dietary supplements (especially the ones known to be toxic for the liver). Indeed, in comparison with these other drugs, OxyElite Pro had not been associated with liver injury at the time. Instead, OxyElite Pro appears to have been the primary cause the QMC doctors seriously considered for their patients, and the only causality assessment they performed.

2. The QMC Doctors' Inconsistently Reported That Patients Were Not Taking Other Dietary Supplements or Drugs.

The charts that the QMC doctors presented to others contained inconsistencies with prior charts. On September 30, 2013, a QMC chart of Patients 1-7 listed 11 dietary supplements besides OxyElite Pro that the patients were taking.[97] The final published version of the chart, on August 2014, listed only four other dietary supplements.[98] An update of the chart, presented at an AASLD meeting on May 4, 2015 listed no other dietary supplements.

The chart never contained the prescription and OTC drugs that the patients were taking. Dr. Wong questioned whether this omission was appropriate: "Should you list all the other meds?"[99] The QMC doctors did not disclose patient use of known hepatotoxic drugs including pain relievers such as acetaminophen, ibuprofen, and naproxen. Acetaminophen especially is a common cause of liver injury, accounting for nearly 50 percent of acute liver failure in the United States, and most cases of drug-induced liver injury.[100] Although many of the patients took acetaminophen, the QMC doctors did not administer N-acetylcysteine (NAC), which is the standard treatment for acetaminophen toxicity and recommended for all cases of suspected herb- or drug-induced liver injury. Indeed, two of the QMC doctors (Drs. Roytman and Tsai) authored a paper on NSAID-induced liver injury that was published in September 2013,[101] which was approximately the same time that they resolved to write a paper about OxyElite Pro. In that publication, they wrote:

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[96] Table 1.

[97] QMC Chart of Patients 1-7 (QC 2492-2501).

[98] Roytman et al., *supra* note 10.

[99] Dr. Wong to Dr. Roytman, Dr. Tsai, and others (Sept. 30, 2013) (QC 2492).

[100] Lee, "Recent Developments in Acute Liver Failure," 26 *Best Pract. Res. Clin. Gastroenterol.* 3 (2012).

[101] A. Marumoto, M. Roytman & N. Tsai, "Trial and Error: Investigational Drug Induced Liver Injury, A Case Series Report," 72 *Hawai'I J. Med. & Pub. Health* 30 (Sept. 2013).

> Although this was not a case of acetaminophen toxicity, N-acetylcysteine was administered given the critical nature of their illness and lack of alternative treatment options. . . . Prompt removal of the offending agent and supportive treatment remain the corner stone of DILI treatment. There is some data to indicate that acetylcysteine is helpful in other types of DILI and should be considered given relatively benign nature of this therapy.[102]

Thus, the QMC doctors knew that NAC should be given in suspected cases of liver injury caused by a drug or dietary supplement. These facts again call into question the QMC doctors' handling of these cases and their analysis of the causality.

3. The QMC Doctors' Statements Became the Basis for Actions by Regulators.

The statements of the QMC doctors served as the basis for statements and actions of the regulatory agencies. For example, in its October 8, 2013 advisory, CDC reported: "There was no other dietary supplement or medication use reported in common by more than two patients."[103] Dr. Park was quoted in a Hawaii DOH news release as stating: "No other supplement or medication has been identified in common among more than two patients."[104] Yet, the records do not support this determination (see Table 1). For example, Patients 1-4 all used acetaminophen; Patient 2 was even diagnosed, by QMC doctors, as having suffered an acetaminophen overdose.

One CDC official questioned the absence of analysis related to other drugs: "some readers might wonder whether concomitant use of acetaminophen-containing products was effectively ruled out especially in view of the recent publicity about liver damage caused by acetaminophen."[105] The CDC authors of the advisory then noted, in an internal email on October 10, that, in fact, nine patients had reported some acetaminophen use.[106] The MMWR abbreviated report from October 11, 2013 claimed that half of the patients that used OxyElite

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[102] *Id.* at 32.

[103] CDC Health Advisory: Acute Hepatitis and Liver Failure Following the Use of a Dietary Supplement Intended for Weight Loss or Muscle Building (Oct. 8, 2013) (DOH 00556-00557).

[104] Hawaii DOH News Release: Department of Health Requests Voluntary Removal of OxyElite Pro Supplement from Sale (Oct. 8, 2013) (DOH 01991).

[105] Email from John S. Moran, CDC, to Joshua Schier and Lauren Lewis, CDC (Oct. 9, 2013) (DOH 00181).

[106] Kevin Chatham-Stephens to Arthur Chang and others (Oct. 10, 2013) (DOH 00180) ("9 reported some use of acetaminophen.").

Pro reported that they did not use other dietary supplements.[107] It is not clear why, given these issues, regulators did not investigate the basis for the QMC doctors' statements further.

On November 6, 2013, FDA repeated the problematic information from the QMC and CDC about other supplements and drugs: "Alcoholic liver disease or acetaminophen ingestion was also ruled out. . . Viral, autoimmune, prescription drug, alcohol, and over-the-counter drugs were ruled out as alternative causes."[108] The FDA relied on the conclusions of the QMC doctors: "Medical records indicate that attending physicians consider OxyElite Pro to be the likely cause of illness in approximately 75% of the cases FDA reviewed."[109]

C. The Documents Do Not Support the QMC Doctors' Assertion that the Patients Suffered from "Acute Liver Failure."

Although the QMC doctors and the press stated that at least five of the QMC patients had "developed acute liver failure,"[110] the existing patient records do not support this assertion. For example, the records of most case patients state that they did not have encephalopathy, and thus did not have "acute liver failure."[111]

The QMC doctors themselves noted this error. On September 28, 2013, they discussed how most of the patients did not have "liver failure."[112] Dr. Tsai stated that they could clarify their earlier statements in the discussion section of the article they would publish.[113]

Despite these statements, Dr. Tsai emailed CDC on October 8, 2015 with details about the QMC poster of eight "acute liver failure cases."[114] The QMC doctors also wrote the following in a January 27, 2014 statement to the Hawaii legislature about OxyElite Pro: "We have

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[107] Park et al., *supra* note 3.

[108] Letter from Michael R. Taylor to USPLabs LLC (Nov. 6, 2013).

[109] *Id.*

[110] Kristen Consillio, "Weight-loss pills may damage liver: doctor" *Honolulu Star-Advertiser* (Sept. 5, 2013).

[111] The QMC doctors knew that the definition of liver failure requires jaundice and encephalopathy, and thus that most of the patients did not actually have liver failure. *See* Email from Dr. Tsai to Dr. Wong, Dr. Roytman and others (Sept. 28, 2013) (QC 2495-2501).

[112] Email from Dr. Wong to Poerzgen, Dr. Tsai, Dr. Roytman and others (Sept. 28, 2013) (QC 2495).

[113] Email from Dr. Tsai to Poerzgen, Dr. Wong, Dr. Roytman, and others (Sept. 28, 2013) (QC 2495-2496).

[114] Dr. Tsai to John Ward, CDC (Oct. 8, 2013) (QC 2577)

experienced an unprecedented number of patients presenting with acute liver failure to our facilities."[115]

The QMC doctors published a more accurate account of liver failure in a scientific journal. In the Roytman Letter to the Editor, they noted that only three patients had liver failure - the two transplants and one death discussed below.[116] However, QMC doctors, media and regulators continued to refer to patients being in "liver failure." For example, an article about Dr. Wong that appeared in *Honolulu Magazine* in June 2014 said that by October 8, 2014 there were 24 cases of "liver failure in Hawaii" linked to OxyElite Pro.[117] On November 18, 2013 FDA wrote that it learned in September 2013 of "seven Hawaii residents with acute liver failure" (Patients 1-7) and that by the end of October 2013 there were 43 Hawaii "cases of acute liver failure."[118]

D. The QMC Doctors Reported Unreliable Causality Scores for Their Patients.

Perhaps the most troubling example of the QMC doctors' analysis is the upgrading of their causality assessment scores. They undertook the scoring after treating the patients in an effort to publish materials supportive of their conclusions. They used the Roussel Uclaf Causality Assessment Method, the leading method for assessing causality in cases of suspected liver injury induced by drugs or dietary supplements. The scores were produced by Dr. Roytman, who had not yet passed her boards,[119] though use of the scale demands expertise. Drs. Wong and Tsai claimed that they did not oversee the scoring, stating that they trusted Dr. Roytman's analysis.[120]

Dr. Roytman testified under oath that she had upgraded the scores to better match her expectations that OxyElite Pro was the cause based on her clinical work with the patients.[121]

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[115] QMC Doctors, Statement re S.B. 2067 (Jan. 27, 2014), http://www.capitol.hawaii.gov/Session2014/testimony/SB2067_Testimony_HTH_01-27-14_.pdf.

[116] Roytman et al., *supra* note 10, at 1298 ("Three patients developed fulminant hepatic failure. Two patients underwent urgent transplantation, and one died.").

[117] D. Thompson, "The Transplant Surgeon Who Went Out On A Limb," Honolulu Magazine (June 2014).

[118] FDA, OxyElite Pro Supplements Recalled (Nov. 18, 2013), http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm374742.htm.

[119] Dr. Roytman wrote: "If I flunk my boards on oct 15, at least I have a shot at 15 seconds of fame:)" Email from Dr. Roytman to Dr. Wong (Sept. 21, 2013) (QC 2397).

[120] Tsai Deposition, at 86:18-22; Wong Deposition, at 103:24-104:8.

[121] Roytman Deposition, at 156:14-158:1 ("Q. So in -- based on your clinical work with these patients, you felt that several of them should have been higher, so you went back and rescored them, and they were then higher? A. That's right.").

The following are some of the examples of these unjustified "upgrades" to reach high causality levels. Positive scores lead to greater assessments of causality with a higher causality grading.

- **Upgrading the RUCAM Item Score to +2 by Ignoring Alternative Causes of Liver Illness.** As explained above, the QMC doctors did not systematically exclude other causes of hepatitis, such as viral hepatitis. Nevertheless, for seven of the original eight patients (all but Patient 4), the QMC doctors reported "+2" -- the highest possible score -- for "Exclusion of other causes of liver injury." Because other causes were evident such as viral infections or overdose on pain medications, the score should have been lower (e.g., "–3"). The probability of these other evident causes is a medical judgment, and it is possible for reasonable experts to disagree about final diagnoses. However, here the QMC doctors did not test -- much less exclude -- important causes of hepatitis. Furthermore, many of their patients tested positive for antibodies to hepatitis-causing viruses, and the QMC doctors did not follow the titer courses (or treat the patients for possible infections). It should be evident, even to those unfamiliar with the test, that there was no basis for Dr. Roytman to upgrade the scores.

- **Upgrading the RUCAM Item Score from Negative to 0 by Ignoring Co-administration of Drugs and Dietary Supplements.** As explained in detail above, the QMC doctors were aware that their patients had taken other drugs and dietary supplements in addition to OxyElite Pro. Nevertheless, for all eight original cases, the QMC doctors inexplicably reported "0" in their RUCAM scoring, indicating no concomitant drugs or "incompatible time to onset." For all patients, the documentation available indicates that the should have been "–1", indicating "concomitant drug with suggestive time to onset." For many of the patients, perhaps the score should have been even lower -- "–2" or "–3". In any event, it is not justifiable, based on the records available, to say that there was no concomitant drug use.

- **Upgrading the RUCAM Item Score to +3 for ALT Course after Cessation of OxyElite Pro.** For seven of the original eight cases (all but Patient 3), the QMC doctors reported "+3" for decrease of alanine aminotransferase (ALT), which is a test to identify liver damage, from peak value following discontinuation of OxyElite Pro in their RUCAM assessment that was the basis for submitting the Roytman Letter to the Editor.[122] This means that they claimed that ALT levels decreased ">50% within 8 days" from the last use of OxyElite Pro. This is an exacting standard, rarely achieved in any case series of suspected herb-induced liver injury and certainly not achieved in the QMC cases. Many of the QMC cases did not even come to the doctor during the first 8 days after they stopped using OxyElite Pro, so the QMC doctors could not have known what happened to

[122] Roytman et al., *supra* note 10.

these patient's ALT levels during that critical window. For example, one does not achieve +3 scores when the dietary supplement use was stopped intentionally two weeks before presentation at a doctor's office or hospital when the first ALT assessment is possible (as was the case for Patient 1 and Patient 7), or by inability to eat and vomiting for two weeks before going to the hospital when a dietary supplement was certainly not consumed (as with Patient 2).[123] As with case 4, treatment with corticosteroids (betamethasone), fexofenadine, and ursodiol during the period after OxyElite Pro was no longer consumed masks ALT decline and does not represent the natural course of ALT decline.[124] In all these circumstances, where assessment is not possible, the score must be 0, not +3. Dr. Roytman admitted in her deposition that she upgraded her scores to better match her expectations.[125] She originally scored seven of the original eight patients at +2, but later for publication upgraded them to +3.[126] Remarkably, she also upgraded Patient 3 from +1 to +2. In other words, she upgraded all her scores by 1 point with very little justification. These methods call these tests and the causality that they represent into question.

- **Upgrading the RUCAM Item Score to +2 for Time to Onset from First Use of OxyElite Pro.** The QMC doctors reported that all eight of the original patients had time to onset of their liver illness after use of OxyElite Pro that was "suggestive." This earned the highest RUCAM level, giving "+2" to each patient It meant that time from the beginning of use of OxyElite Pro was "5 to 90 days and [the patients were] still receiving the medication." For some patients, such as Patient 2, no data were provided about the time of illness. Therefore, no assessment for this item in the RUCAM score should have been possible. Other patients had been taking OxyElite Pro without illness for much longer than 90 days. USPlabs only began to distribute aegeline-containing dietary supplements in late 2012; but the QMC doctors did not know when patients switched from DMAA-containing OxyElite Pro, and this uncertainty should have been reflected in the RUCAM score.

These four upgrading steps, at their maximum, produce a RUCAM score of +7, which was the score (calculated with exactly these steps) that the QMC doctors reported for Patients 1, 2, 5, 6, and 7.

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[123] *See* Teschke et al. (2016), *supra* note 11; Teschke et al. (2015), *supra* note 11.

[124] *See* Teschke et al. (2016), *supra* note 11.

[125] Roytman Deposition, at 156:14-158:1.

[126] The final RUCAM scores accompanied the case report forms for Patients 1-8, *supra* note 59. For the original chart with all patients scored 1 point lower, see QMC Chart of Patients 1-7 (QC 2492-2501).

Patient 8 was given the highest score: +10. This was the only case reported as "highly probable." Patient 8's case is explained more fully in the published peer-reviewed article by Professor Rolf Teschke and his colleagues.[127] Cited repeatedly and approvingly by the QMC doctors, the Hawaii DOH, and CDC in 2013 and 2014,[128] Teschke and his colleagues are the world's leading experts on the RUCAM scale. Teschke and his colleagues criticize the QMC analysis and explain in their 2015 publication that Patient 8 should have been scored at only +1 for OxyElite Pro. In fact, they concluded that the patient appeared to have overdosed on naproxen.

Although we did not learn about it until mid-2015, the QMC tested Patient 8 for genetic sensitivities and found that this patient tested positive for sensitivity to naproxen,[129] providing further evidence for the conclusion by Teschke and his colleagues. Unlike the 2013 and 2014 published reports by the QMC doctors, which gave only the final RUCAM scores[130], the paper by Teschke and his colleagues presented all underlying data for public scrutiny.

IV. THE QMC DOCTORS' ERRONEOUS FINDINGS CONTINUE TO APPEAR IN THE SCIENTIFIC AND REGULATORY DISCUSSIONS ABOUT OXYELITE PRO.

A. The Klontz (2015) Article

A 2015 article by Karl Klontz and others at FDA reviewed 21 medical records submitted from the Hawaii DOH.[131] These records originated with the QMC doctors. For example, the Klontz article reports that the QMC doctors notified FDA in September 2013 "of seven previously healthy adults who developed acute or fulminant non-viral hepatitis after ingesting OxyELITE Pro."[132]

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[127] Teschke et al. (2015), *supra* note 11.

[128] *See* discussion of citation on Teschke's articles by CDC, Hawaii DOH, and the QMC doctors *supra* note 60.

[129] Companion Dx Pharmacogenomics Testing on Patient 8 (QC 959-968). The company that performed the testing appears to have been incorporated on September 4, 2013 -- the day Dr. Wong went to the media with her original story -- by one of the co-authors on the Roytman Letter, Peter Bryant-Greenwood.

[130] A case report form (CRF) was completed for each of the QMC case patients. *E.g.*, CRF for Patients 1-8 (QC 851-52, 871-72, 894-95, 901-02, 923-24, 940-41, 947-48, 955-56).

[131] K. Klontz et al., "The Role of Adverse Event Reporting in the FDA Response to a Multistate Outbreak of Liver Disease Associated with a Dietary Supplement," 130 *Public Health Reports* 526 (Sept.-Oct. 2015). Note that, while the authors have FDA affiliations, they expressly disclaimed the views in the paper as the views of the FDA.

[132] *Id.*

As we explain above and in Table 1, these original seven patients (as well as Patient 8) were not "previously healthy," and the QMC did not exclude the common viral causes of hepatitis carefully or completely. We have records for the other thirteen Hawaii patients as well -- the other patients where the QMC doctors gave information to the Hawaii DOH who in turn gave it to FDA. They are even weaker cases. The Klontz article thus suffers from the same problems as the regulators' statements discussed above, i.e., it is founded on QMC's analysis, not on the complete medical records of each patient. The Klontz article describes reports of liver disease "in the absence of viral infection" and other known causes of liver damage, but the QMC files provide clear evidence to the contrary. All such reports from Hawaii are therefore highly unreliable.

The epidemiological curves and the reporting information in the Klontz article also present problems. On October 22, 2013, CDC wrote that the epidemiological curves are shaped by the public health alerts and the media: "We assume the epi curves are influenced by the alerts and recall bias of the reporting clinicians. Symptom onset data was also limited by poor patient recall."[133] As shown in the Klontz article, FDA received only two MedWatch reports for liver disease designated by the authors as likely due to OxyElite Pro ("liver-related reports") before September 2013 -- one from February and one from March. Notably, FDA received not a single liver-related report between March and September 2013, although aegeline-containing OxyElite Pro was sold during that time. Then, with media and regulatory attention -- starting September 5, 2013 and accelerating on September 25, 2013 -- FDA received 27 liver-related reports in September and October. We know that many of the MedWatch forms were submitted by QMC staff. The rest are the expected consequence of the QMC-induced publicity.

We can speculate about the number of liver-related MedWatch reports about OxyElite Pro that would have been submitted to FDA had the QMC doctors' analysis and approach not suffered from the aforementioned deficiencies. Our best guess is 0-2 cases a year, which is consistent with the number of reports from 2010 through September 2013 as shown in the Klontz article, and about as many as you might expect from a top-selling dietary supplement like OxyElite Pro. Unsurprisingly, October and November 2013 also saw a spike in non-liver-related MedWatch reporting related to OxyElite Pro, which can also be attributed to the widespread publicity surrounding the dietary supplement.

Although in late 2013, USPlabs stopped using aegeline in its products and stopped selling OxyElite Pro in the United States, the company continues to believe that the science supports the fact that OxyElite Pro was always safe, and has not caused any adverse hepatic events. The excess reported cases from September-December 2013 are best explained by the media attention surrounding the patients in QMC hospital. This hypothesis is strengthened by FDA's own research since 2013. As Klontz reports in his article, no contaminants were found in OxyElite Pro.[134] In addition, the ingredients in OxyElite Pro, including aegeline, have not been

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[133] Email titled "RE: CDC Acute Hepatitis (associated with OxyElite Pro) Case Update" (Oct. 22, 2013) (DOH 04792-04795).

[134] *Id.*

found to be toxic to the liver. Indeed, an FDA-sponsored study published in August 2015 found that aegeline, a component of the fruit of the Bael tree that is widely consumed throughout the world, is "reported to have a high nutritional value and many perceived health benefits."[135] The article found no evidence of aegeline toxicity in its scientific tests, although it cites the 2014 Roytman Letter as evidence of possible toxicity.[136] There is no sound scientific evidence that the Bael fruit or aegeline are poisonous or dangerous.[137] Bael products continue to be sold on the Internet today without FDA action.

B. The Johnston (2015) Article

In the fall of 2015, led by David Johnston of the Hawaii DOH, the regulators published an article based on the QMC cases and other Hawaii cases in *Drug Testing and Analysis*.[138] This article had been submitted to other journals, and was rejected several times in 2014.[139] Then, on December 22, 2014, Dr. Wong emailed Johnston, offering to contact Pieter Cohen, a physician and strident critic of the dietary supplement industry, for help with finding a journal that would take it.[140] On January 28, 2015, Johnston announced to his co-authors that he found a solution: Dr. Cohen wanted to publish the Johnston article in "a special edition of 'Drug Testing and Analysis'" that he was "putting together," which would focus on the dangers of dietary supplements.[141]

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[135] V.K. Manda et al., "Inhibition of CYP3A4 and CYP1A2 by Aegle marmelos and its constituents," *Xenobiotica*, Early Online 1-9 (Aug. 2015). This study was supported by a grant from FDA (grant number 1U01FD004246-04).

[136] *Id.*

[137] Indeed, the bael fruit is thought to have a beneficial effect. *Id.* The QMC's findings are the only basis for the belief that aegeline is dangerous.

[138] D. Johnston et al., "Hepatotoxicity associated with the dietary supplement OxyELITE Pro™ — Hawaii, 2013," *Drug Test. Analysis* (2015).

[139] Email from Johnston to Dr. Wong (Dec. 18, 2014) (WONG 00338).

[140] Dr. Wong offers to send it to Pieter Cohen "for an opinion," explaining he has "even been on the Dr. Oz show" about dietary supplements, and he "has some pull with the editors" of some journals. Email from Dr. Wong to Johnston (Dec. 18, 2014) (WONG 00337-338).

[141] Email from Johnston to Dr. Wong and others (Jan. 28, 2015) (WONG 00341-342) ("I just wanted to let you all know that we have identified another journal to submit our OEP manuscript to. Dr. Pieter Cohen reached out to us about a special edition of "Drug Testing and Analysis" that he is putting together that will be focused on issues surrounding supplements. After talking to him and sharing our manuscript with him he felt it would be a good addition to the issue and so we are going to go ahead and submit it.").

In the Johnston article, the regulators, plus Dr. Wong as a co-author, claimed to have identified 36 cases that met their case definition and said they took OxyElite Pro. The QMC cases are the core cases,[142] especially the original eight patients reported in the Roytman Letter to the Editor, which the regulators used to design their case definition. Relying on data from the QMC doctors, the Johnston article makes unsupported statements about the Hawaii cases.

The authors of the Johnston article were unaware of the many other dietary supplements as well as the OTC and prescription drugs that the patients were taking.[143] Although the Johnston article reports that most of the OxyElite Pro cases also took at least one other dietary supplement, we know this is an underestimate. The article states: "Only one other supplement for weight loss or muscle gain was common to multiple cases." In fact, there were several common supplements even among the first few patients (see Table 1). For example, as noted above, Patients 1 and 4 both purchased CLK and Super HD (weight-loss dietary supplements) multiple times in the months prior to their liver illnesses, including each within a month of illness onset. It also appears that the information that the QMC doctors shared with the regulators did not show the other drugs and supplements that the case patients were taking (see Table 1). Thus, the statement in the Johnston article about the lack of supplement use by the Hawaii patients is inconsistent with the records and documents for these patients.

Based on their interviews with case patients, the authors of the Johnston article knew that at least 30 percent of the patients took Tylenol (acetaminophen) and 41 percent took nonsteroidal anti-inflammatory drugs (NSAIDs) in the weeks before their illnesses. Acetaminophen accounts for nearly 50 percent of cases of acute liver failure annually, and the vast majority of cases of drug-induced liver injury.[144] NSAIDs are associated with 10 percent of cases of drug-induced liver injury.[145] Many (if not most) of the Hawaii cases -- and certainly many of those that are not explained by viral hepatitis or autoimmune hepatitis -- may be due to acetaminophen and/or NSAID use. Indeed, the regulators own estimate of acetaminophen use

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[142] Table 1 contains more information about Patients 1-8. We have created a table with more than twenty additional QMC patients, which we can share upon request.

[143] The authors of the Johnston article complained among themselves that patients were so biased by the doctors that they would not admit to taking other supplements. Email from Sarah Park to Lauran Lewis, CDC, and others (Oct. 1, 2013) (DOH 02532; 02534) ("it does appear that despite our best efforts, the public is already biased (mostly by their clinicians) in thinking that OEP is the culprit as it's difficult to get them to identify other supplements they may be taking concurrently."). The authors decline to mention this pervasive bias in their published article.

[144] W.M. Lee, "Recent Developments in Acute Liver Failure," 26 *Best Pract. Res. Clin. Gastroenterol.* 3 (2012).

[145] F. Bessone, "Non-Steroidal Anti-Inflammatory Drugs: What Is the Actual Risk of Liver Damage," 7 World J. Gastroenterol. 16 (2010).

suggests that 30 percent of the cases attributed to OxyElite Pro may actually have been due to acetaminophen, and many others were likely due to NSAID use.

The regulators' estimate of acetaminophen use may be an underestimate. The regulators collected their data using the DOH questionnaire for OxyElite Pro. That survey asked patients whether they took OxyElite Pro, followed by a page of questions about OxyElite Pro, before generally asking patients to list the dietary supplements or drugs they were taking.[146] The only other dietary supplement or drug that was asked about by name was "Tylenol." The DOH questionnaire asked only about "Tylenol"[147] the brand, not acetaminophen generally. Tylenol sales were less than a quarter of the acetaminophen market by 2012.[148] By asking only about "Tylenol," regulators likely missed much of the acetaminophen use among the Hawaii patients. Dr. Park emailed Dr. Wong on November 25, 2013 about the problems with the survey:

> Forgot to mention, apparently, our questionnaire asked specifically about tylenol usage as opposed to "acetaminophen." It was felt that people would be better likely to recognize the former than the latter. That honestly didn't sit all that well with me . . . .[149]

Dr. Wong agreed: "It's true that more will recognize tylenol but still need to ask them about the others. I usually have to ask the questions several times and make them think before

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[146] The questionnaire began asking about dietary supplements as follows: "During the 2 months before your symptoms began, did you take any dietary, nutritional, or herbal supplements? This includes things like vitamins, calcium pills, weight loss pills, any products made at home, etc." Email from David Johnston to Sarah Park and Melissa Viray (Oct. 21, 2013) (DOH 02807; 02812) (attaching the most current versions of the questionnaire, file dated September 30, 2013). If the answer to this question was "yes," instead of asking the patients to list the supplements they took, the questionnaire immediate proceeds to more than a page of questions about OxyElite Pro. Only after all of the OxyElite Pro questions are finished, does the questionnaire ask the following question: "Please provide the following information for any other supplements you have taken during the 2 months before your symptoms began. Remember this includes things like vitamins, calcium pills, weight loss pills, any products made at home, etc" The questionnaire then asked a series of short questions about Tylenol, "over-the-counter or prescription medications," cigarette/tobacco use, and illicit drug use.

[147] *See* DOH 02814.

[148] *See* Reuters, "Hey, where's my Tylenol? CVS pulls popular pain-reliever from some stores," *Daily News* (Jan. 15, 2013), *available at*

http://www.nydailynews.com/life-style/health/cvs-won-stock-tylenol-stores-article-1.1240622.

[149] Email from Park to Dr. Wong (Nov. 25, 2013) (WONG 00197).

answering. . . . they barely remember the stuff like tylenol and OTC stuff."[150] Their co-authors tried to alleviate their concerns by saying they checked the medical records for acetaminophen,[151] but OTC drugs like acetaminophen are often not recorded in medical records.[152] Although Drs. Wong and Park agreed the lack of questioning about acetaminophen was a problem, they apparently decided not to press the issue and resolved to be better in the future: "yep. agreed. we'll probably get nit-pickier about things for the case-control study we're planning. . . ."[153]

There were also pre-existing but previously undiagnosed autoimmune liver disease. Autoimmune hepatitis is a common cause of acute liver failure and other liver injuries.[154] It causes 11-20 percent of cases of chronic hepatitis.[155] The regulators reported in the Johnston article that many of their cases had evidence of autoimmune hepatitis: "almost a third of our cases demonstrated positive autoimmune markers; however, the significance is unclear."[156] And this number is an underestimate of the number of patients with autoimmune hepatitis (AIH) since a "work-up for less common causes of acute fulminant hepatitis (e.g. autoimmune markers, hepatitis E serologies) was performed at the discretion of the diagnosing physician."[157] As shown above, the QMC doctors did not investigate this cause.

The regulators did not exclude these AIH cases from their tally of OxyElite Pro cases. If a case reported use of OxyElite Pro, the regulators included the patient as a case of possible drug-induced liver injury, even if there was strong evidence for autoimmune disease or other etiologies.[158]

In the case definition, the authors explained that they included in their case series patients with chronic liver disease so long as the diagnosis was not "pre-existing."[159] This "pre-existing" criterion lacks foundation. Liver disease is often diagnosed when a patient comes to

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[150] Email from Dr. Wong to Park (Nov. 25, 2013) (WONG 00197).

[151] Email from Park to Dr. Wong (Nov. 25, 2013) (WONG 00197).

[152] As OTC drugs, they would not appear in records of prescription drugs.

[153] Email from Park to Dr. Wong (Nov. 25, 2013) (WONG 00196).

[154] Lee et al., *supra* note 144.

[155] H.I. Fallatah & H.O. Akbar, "Autoimmune Hepatitis as a Unique Form of an Autoimmune Liver Disease: Immunological Aspects and Clinical Overview," 2012 Autoimmune Diseases 312817 (2012).

[156] Johnston, *supra* note 138.

[157] *Id.*

[158] *Id.*

[159] *Id.*

the doctor with symptoms, not before. Many of the cases attributed to the use of OxyElite Pro may instead have been suffering from autoimmune liver illness unrelated to any drug or dietary supplement.

In addition, the Johnston article claims to have excluded only three of the nine key hepatitis-causing viruses. The regulators focused on hepatitis A, B, and C. (Specifically they included cases with "no evidence of acute hepatitis A or acute or chronic hepatitis B and C infection."[160]) The regulators' case definition did not require the other six common viral causes of hepatitis to be excluded.

The documents show that the later findings and articles produced were based on the statements of the QMC doctors. This raises a serious question as to whether the liver injuries among the cases identified in the Johnston article are best explained, not by OxyElite Pro, but by the patients' various exposures to pain medications such as acetaminophen and NSAIDs, as well as to viruses and other pathogens and autoimmune hepatitis. Table 1 contains more information about the eight key cases (Patients 1-8).

C. Details Regarding the Two Transplants and One Death

The QMC doctors and the regulators have repeatedly cited the two patients who received transplants and the one who died. As discussed above, these are the only three patients who met the definition of "acute liver failure." Most of the other Hawaii patients merely had transiently elevated liver enzymes. All patients but these three recovered.

The QMC doctors wanted to "concentrate on the initial dramatic cases" to write a "compelling story."[161] Dr. Wong wanted to include the death case in the QMC case series, even before they had any of the patients' lab values, because that case "will highlight the danger of the drug."[162] The regulators similarly cite these patients as examples of the alleged dangers OxyElite Pro. The regulators did this first in their announcements on October 8, 2013[163] and

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[160] Johnston, *supra* note 138.

[161] Email from Dr. Roytman to QMC colleagues (Oct. 9, 2013) (WONG 00087).

[162] Email from Dr. Wong to Poerzgen, Dr. Tsai, Dr. Roytman and others (Sept. 28, 2013) (QC 2504).

[163] FDA MedWatch, OxyElite Pro: Health Advisory—Acute Hepatitis Illness Cases Linked to Product Use (Oct. 8, 2013) ("two cases have received liver transplants and one person has died."); CDC Health Advisory: Acute Hepatitis and Liver Failure Following the Use of a Dietary Supplement Intended for Weight Loss or Muscle Building (Oct. 8, 2013) ("One patient died, and two patients received liver transplants.") (DOH 00556-00557); Hawaii DOH, Medical Advisory UPDATE: Acute Hepatitis and Liver Failure Potentially Associated with Ingestion of Dietary Supplements (Oct. 8, 2013) ("one patient has expired, two received liver transplants") (DOH 429-430).

continually thereafter. For example, Johnston (2015) wrote: "Two of the OEP-exposed case required liver transplants and one OEP-exposed case died."[164]

Documents indicate that apparently two of the three did not ever take OxyElite Pro and all three patients had other obvious causes for their liver illnesses.

1. The First Transplant

Dr. Wong met the first transplant case ("Patient 1") on September 3, 2013, which was the day before she went to the media. She later described the patient to the media as "a young bodybuilder who had been rushed to Honolulu by air ambulance from the Big Island,"[165] who was "previously healthy."[166]

The QMC patient records contradict these assertions. They show that Patient 1 was not a healthy young bodybuilder, but was morbidly obese, drank regularly, used chewing tobacco, and had rashes all over his body, including his feet and sacrum.[167] Between 1997 and January 4, 2013, Patient 1 logged 22 visits to the emergency room. These visits were prompted by severe asthmatic episodes,[168] allergic reactions, severe rashes,[169] severe headaches,[170] severe fungal infections, and brachial neuritis. His asthma has been treated with many drugs, including steroids.[171] Upon his admission to Kona Community Hospital on August 25, 2013, an abdominal CT scan revealed evidence of a thickening of the gallbladder wall and cirrhosis with

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[164] Johnston, *supra* note 138.

[165] D. Thompson, "The Transplant Surgeon Who Went Out On A Limb," *Honolulu Magazine* (June 2014).

[166] Roytman et al., *supra* note 10.

[167] *See Table* 1; Expert Report of Robert G. Gish, M.D. (Sept. 22, 2015).

[168] One such episode was described by Patient 1 as being similar to a heart attack: "I overexerted myself one [football] practice and I got like a heart attack kind of. I was rushed to Waimea hospital, Kamuela hospital." Patient 1 Deposition, 46:24-47:1.

[169] Patient 1 Deposition, at 265:21-265:6, 266:25-267:5 (describing an ER hospital visit for a rash: "Q. So this must have been a pretty severe rash if – you went to the emergency room for it? A. Yes. . . . Q. So you were prescribed Vicodin for that rash? A. Oh, okay. Q. That must have been a pretty painful rash. A. Yes, it was. Q. Did the Vicodin help? A. Yes.").

[170] Patient 1 described the pain level for several of these headaches to be a "10 out of 10", which signified that it was the "most pain" he ever experienced. Patient 1 Deposition, at 240:3-240:17.

[171] Patient 1 testified that he has been taking prednisone from at least 1997 through the date of his second deposition in July of 2015. Patient 1 Deposition, at 296:24-297:18.

ascites.[172] Patient 1 was also previously diagnosed with atopy -- a predisposition to allergic hypersensitivity. When rejecting the QMC doctors' paper, the *New England Journal of Medicine* told them that their paper must disclose if a patient was diagnosed with atopy, which the QMC doctors did not do.[173]

Patient 1's medical records were consistent with an active viral infection, which likely caused his liver illness. Around the time of liver failure in 2013, the patient tested positive for CMV, EBV, and VZV. The patient was not tested properly for hepatitis E.[174] The QMC doctors did not assess titer changes for any these viruses over time as standards of care require, though this patient appeared to be suffering from an active infection.[175] Throughout September 2013, Patient 1 had elevated monocytes in the blood, an indicator of viral infection. His liver enzyme levels did not decline steadily after ceasing OxyElite Pro use, as one would expect if his injury was drug induced. Instead, his liver enzyme levels undulated, and those undulations continued post-transplant. Patient 1 had potential exposure to viral pathogens, other infectious agents, and environmental toxins through hunting and eating of wild hogs and work as a coffee farmer.[176] Had the QMC doctors investigated Patient 1's signs of active viral infection (and other possible causes) and treated this patient appropriately, he may not have needed a liver transplant.[177]

Patient 1 had other illnesses and health issues that would have required other drugs that could have caused or contributed to his liver problem. He had a severe and persistent (and sometime debilitating) fungal infection on both feet -- from 2011 until 2013 -- with open sores and scabbing.[178] Treatment for these infections including prescription pain medication containing acetaminophen, such as Vicodin (acetaminophen/hydrocodone) and Percocet (acetaminophen/oxycodone),[179] and the antibiotic Bactrim (trimethoprim and sulfamethoxazole), to which he developed a rash around the time of his liver injury.[180] Although Patient 1 also took many drugs that contained acetaminophen, and acetaminophen causes half of all cases of liver

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[172] Kona Community Hospital records for Patient 1 (Kona 53-54).

[173] Reviewer Comments (Dec. 16, 2013) (QC 3157) ("Evidence of a history of allergy or atopy . . . should be documented").

[174] Anti-HEV-IgG and HEV PCR were not assessed in this patient. *See* Table 1; *see also* Teschke et al. (2016), *supra* note 11.

[175] *See* Teschke et al. (2016), *supra* note 11.

[176] Expert Report of Robert G. Gish, M.D. (Sept. 22, 2015); Table 1.

[177] Teschke et al. (2016), *supra* note 11.

[178] Patient 1 Deposition, 265:1-266:12 (describing the "open wound on [his] foot"); *see* Table 1.

[179] Patient 1 Deposition, 266:25-267:5; Expert Report of Robert G. Gish, M.D. (Sept. 22, 2015).

[180] Transplant Surgery Progress Note (QMC 1779-1780; Patient 1 5926-2928).

failure,[181] Patient 1 was not given NAC, the recommended treatment.[182] Patient 1 used Advair (fluticasone propionate and salmeterol) two times daily and refilled a prescription for Advair and ProAir (albuterol sulfate) three days before admission to the hospital for liver illness. Patient 1's medical record warns against use of pain medication (e.g., acetaminophen) with steroids (e.g., certain asthma medications).[183]

Patient 1 took many other supplements besides OxyElite Pro. According to purchase records and medical records, Patient 1 had consumed the following dietary supplements between March 2013 and the onset of liver illness in the summer of 2013: Beyond RAW Re-GROW; CLK, CLK/Super HD Combo Kit; Green Coffee Bean; Kre-Alkalyn EFX; OxyElite Pro; Preworkout Sample Pack; Pro Performance AMP Wheybolic Extreme 60; Pump-HD; Ripped Freak; Super HD; and Versa-1.[184] The QMC doctors only publically reported one of these other supplements -- Versa-1, which was also distributed by USPlabs.

Given the evidence of infection by three of the nine most common viral causes of hepatitis and this patient's use of acetaminophen and other drugs and dietary supplements, it is difficult to understand how the QMC doctors concluded that this patient's illnesses were "probable" and gave the patient a RUCAM score of +7. It is also questionable as to why the QMC doctors calculated this patient's RUCAM score at all, because there was no real evidence to connect OxyElite Pro to Patient 1's liver issues.

2. The Second Transplant

The second of the two transplants—patient 2—has a remarkable story. According to several QMC medical notations, the QMC doctors concluded that this patient suffered from liver failure caused by an overdose of acetaminophen. This conclusion is supported by the patient's medical records. She was regularly taking not only acetaminophen-containing prescription drugs but also acetaminophen-containing OTC drugs (along with other pain medication). Because acetaminophen causes half of all liver failures in the United States[185] and this patient was taking dangerously high levels of acetaminophen, the correct diagnosis was clear and was made by the QMC. Only later, days after this patient's liver transplant, did the QMC doctors switch their diagnosis from hepatotoxicity caused by an overdose of acetaminophen to hepatotoxicity caused by small amounts of OxyElite Pro. This is surprising since acetaminophen is the most notorious cause of liver failure in the world yet OxyElite Pro only became associated with liver illnesses because of the QMC.

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[181] Lee, *supra* note 144.

[182] See discussion of NAC in text accompanying *supra* notes 101-102.

[183] QC 861-869.

[184] *See* Table 1.

[185] Lee, *supra* note 100.

Furthermore, it is doubtful that patient 2 even took OxyElite Pro. Patient 2 arrived at the QMC in late August 2013, around the time the QMC doctors started to ask everyone whether they used OxyElite Pro. This patient said "no" several times.[186] It was not until after Patient 2 received her transplant, and after repeated questioning from the QMC doctors, that Patient 2 finally "admitted" to taking OxyElite Pro.[187] She reported this OxyElite Pro use after seeing news reports while at the QMC. However, Patient 2 has no proof of purchasing OxyElite Pro, such as possession of the product itself or a receipt for the same. Patient 2 states that she obtained OxyElite Pro "from a friend."[188]

Patient 2 did, however, take large amounts of acetaminophen that caused liver failure. There is abundant evidence of this acetaminophen overdose in her records. For example, an empty bottle for Tylenol, the most popular OTC brand of acetaminophen, was found in her car at the time of her liver illness.[189] In addition to consuming acetaminophen as Tylenol, this patient took other prescription medications that contained acetaminophen and may also have taken other acetaminophen-containing OTC drugs. Before her liver illness, she filled multiple prescriptions for acetaminophen/hydrocodone (a generic version of Vicodin). The version she took contained 500 mg of acetaminophen (the amount in Extra Strength Tylenol) along with 5 mg of hydrocodone (an opioid).[190] The prescription instructed her to take 1 tablet every 4-6 hours. She had been regularly taking acetaminophen/hydrocodone for pain since at least August 2009.[191] Use of this acetaminophen-containing pain medication, especially coupled with the Tylenol use, would have led to unsafe levels of acetaminophen. FDA has warned against liver damage caused by excessive acetaminophen use in OTC and prescription products. In 2011, FDA even asked manufactures to stop making products like the acetaminophen/hydrocodone combination that patient 2 was taking because they were so dangerous; the agency requested that manufacturers to limit levels of acetaminophen in multi-active-ingredient products to less than 325 mg per tablet by 2014.[192] FDA explained:

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[186] QMC Records for Patient 2 (QMC 130, 543).

[187] "Initially denied dietary supplements, but later confirmed." Email from Curtis Toma to Sarah Park (Sept. 19, 2013) (DOH 03101-03103).

[188] Case Report Form (QC 871).

[189] QMC Records for Patient 2 (QMC 260).

[190] See Walgreens Pharmacy Records for Patient 2.

[191] *Id.*

[192] Acetaminophen Prescription Combination Drug Products with more than 325 mg: FDA Statement - Recommendation to Discontinue Prescribing and Dispensing (Jan. 14, 2014), http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm381650.htm.192

> Further, limiting the amount of acetaminophen per dosage unit will reduce the risk of severe liver injury from inadvertent acetaminophen overdose, which can lead to liver failure, liver transplant, and death. . . . Many consumers are often unaware that many products (both prescription and OTC) contain acetaminophen, making it easy to accidentally take too much.[193]

The records show that Patient 2 also had a health history that could have contributed to the risks associated with acetaminophen use. Formerly morbidly obese, she had gastroplasty (stomach stapling) in 2012 that resulted in a 90-pound weight loss, which the QMC noted is a risk factor for acetaminophen toxicity.[194] In a pathology report from August 29, 2013 (two weeks before she stated she had taken OxyElite Pro), one of the QMC doctors wrote: "Consideration of acetaminophen toxicity is warranted given the patient's history of gastric sleve/gastric bypass procedure – a known risk factor for such toxicity."[195] On September 11, 2013 -- two days after the patient's transplant and one day before she stated she used OxyElite Pro -- the QMC doctors concluded: "Assessment: This is 31 year old female patient had liver transplant 9/9/2013 due to acute liver failure from accidental acetaminophen overdose in the setting of gastric bypass."[196]

Despite diagnosing the patient correctly as having overdosed with acetaminophen, the QMC doctors did not give Patient 2 NAC, the standard treatment for all cases of drug-induced liver injury but especially those suspected to be caused by acetaminophen. They did not treat her for an acetaminophen overdose at all. Instead, the patient's liver failed, and she underwent a live transplant at the hands of the QMC. Then, abruptly after the transplant, this patient became an OxyElite Pro case. The QMC doctors concluded that OxyElite Pro was the cause of the liver issue, and used Patient 2 in their published case series, which became the basis for the alarm regarding OxyElite Pro.

In addition to acetaminophen, Patient 2 also regularly took ibuprofen for pain,[197] and may have taken other pain medications. The patient's boyfriend testified that the patient took a lot of identified "migraine medicine"[198]; and the doctor reported "Lot of unidentified medications for

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[193] *Id.*

[194] Bryant Greenwood, Pathology Report (Oct. 29, 2013) (QC 876).

[195] *Id*.

[196] Russell Wong, QMC, Progress Notes for Patient 2 (Sept. 2, 2013) (QMC 483).

[197] CVS Pharmacy Records for Patient 2.

[198] QMC Records for Patient 2 (QMC 260).

headaches."[199] These NSAIDS and unidentified headache medications—which may have been yet another source of acetaminophen—could have contributed to the liver damage.

Patient 2 also took other dietary supplements. According to purchase records and medical records, the patient had consumed the following dietary supplements prior to liver illness: Mega Men Perform & Vitality; Mega Men Sport Vitapak; Amino Energy; Stby Isopure; and Alph Isopure. After liver transplant, in 2014, patient purchased Pro Performance AMP Ripped Vitapak; BPI A-HD; and Neon Sport Intercept.[200] She also continued to take acetaminophen at this time.[201]

Like the first transplant, the QMC doctors concluded that Patient 2's illness was "probably" due to OxyElite Pro, and they assigned her the same unsupportable RUCAM score as Patient 1: +7.

3. The One Death Case

Patient 7, the one death case, has medical records that indicate in multiple places that she took Oxy-Cleanse, a popular cleanser for the intestinal tract distributed by Earth's Bounty.[202] Both Patient 7 herself and her family informed the doctor she took Oxy-Cleanse.[203] For example, one of the records states: "She is taking a cleansing formula called OxyCleanse, which the family is bringing in. Family does not know of any other herbs she may be taking."[204] Notably on September 22, 2013, when this patient was transferred to Honolulu, where the QMC doctors were asking about OxyElite Pro consumption, this patient's family suddenly stated that Patient 7 took OxyElite Pro.[205]

There is no proof of purchase, and no evidence that this patient took OxyElite Pro. In addition, several facts suggest that Patient 7 has not taken OxyElite Pro. Before she encountered the QMC doctors, Patient 7's medical records clearly identify the supplement she took as a "cleansing formula."[206] While both Oxy-Cleanse and OxyElite Pro have "Oxy" in their

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[199] *Id.*

[200] GNC Purchase Records for Patient 2.

[201] *See* Primary Care Physician (Roy Koga, MD) Records for Patient 2 (Koga 85).

[202] "Oxy-Cleanse,' http://www.earthsbounty.com/cgi-bin/commerce.cgi?preadd=action&key=1010-OXY_CLEANSE.

[203] Maui Memorial Medical Center Records for Patient 7 (MMMC 41); Kaiser Permanente Medical Records for Patient 7, Vol. 1 (001236).

[204] Kaiser Permanente Medical Records for Patient 7, Vol. 1 (001236).

[205] Kaiser Permanente Records for Patient 7 (Kaiser Permanente Vol. 2 Page 3)

[206] Kaiser Permanente Medical Records for Patient 7, Vol. 1 (001236).

names, only one -- Oxy-Cleanse -- is marketed and used for cleansing. It seems unlikely that both the patient and her family would make a mistake as to not only the name, but also the intended use of the dietary supplement she was taking. This indicates that Patient 7 was taking Oxy-Cleanse and not OxyElite Pro.

Because the Patient 7 reported consumption of Oxy-Cleanse, she should not have become an OxyElite Pro case patient at all. Instead, she became the most prominent example of the dangers of OxyElite Pro. This patient was not originally part of the QMC case patient series. Dr. Wong advocated for her inclusion to make the cases seem more serious: "I would like to include the one that just got into the ICU.....this will highlight the danger of this drug. I have a feeling that she's going to die.....she's going down quickly."[207]

As with the other patients, the QMC doctors' presentation of Patient 7's case history is inconsistent with the evidence. She was reported to be "previously healthy" at the time of her liver injury and death, but she had nuclear grade 3 ductal carcinoma cancer,[208] a high-grade cancer with a poor prognosis. This patient also had a long history of abusing illegal drugs, including cocaine and methamphetamine.[209] It is possible that her liver damage and impaired mental state was due to intoxication and her history of substance abuse.

As with the other patients, the QMC doctors did not exclude other causes of liver illness for Patient 7, including Wilson's disease, hepatitis E, and VZV. These causes can be treated if diagnoses are considered and established. Wilson's disease was not excluded as none of the following were collected: copper excretion (24-hour urine), copper blood levels, hepatic copper content, rhodanine staining for copper in liver biopsy, examination for Coombs-negative hemolytic anemia and Kayser-Fleischer rings (slit-lamp examination), neurologic-psychiatric work-up, and genotyping.[210] In addition, hepatitis E was not excluded. Acute VZV was also not excluded, because the QMC doctors did not test for negative VZV while VZV IgG was positive.[211]

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[207] Email from Dr. Wong to Poerzgen, Dr. Tsai, Dr. Roytman and others (Sept. 28, 2013) (QC 2504).

[208] Patient 7, Biopsy Report (Sept. 28, 2013) (QMC 237-245)

[209] Expert Report of Robert G. Gish, M.D. (Sept. 22, 2015). In September 2013, at the QMC, she or her family requested substance abuse intervention based on her recent history or current use of "street drugs" and/or alcohol (QMC 744).

[210] Practice guidelines say that Wilson's disease should be considered in any individual between the ages of 3 and 55 years with liver abnormalities of uncertain cause, though age alone should not be used to exclude Wilson's disease. E. Roberts & M. Schilsky, AASLD Practice Guidelines: "Diagnosis and Treatment of Wilson Disease: An Update," 47 *Hepatology* 2089 (2008).

[211] Table 1.

Although it was documented that Patient 7 "will need liver biopsy,"[212] this was not done because the doctors were "convinced" that the illness was due to OxyElite Pro. They wrote on September 26, 2013: "Since patient will likely need sedation for liver biopsy by IR and this may worsen mental status, I would recommend holding off liver biopsy for now. Especially that we are convinced that the cause of the liver failure is due to OxyElite Pro."[213]

The family of Patient 7 questioned this approach. On October 3, 2013, they asked various questions of the QMC doctors, including: "Why haven't you biopsied the liver?"; "Can she be transferred to a different state so that she can get a transplant there? Why isn't Queen's helping us out with this?"; ""Shouldn't someone have been checking her ammonia? She was talking normally before she came down here!"[214] It is not clear if the family ever received satisfactory answers to their questions, and the patient died soon after.

Like the two transplants, the QMC doctors concluded that Patient 7's illness was "probably" due to OxyElite Pro, and assigned the same problematic RUCAM score: +7. It is difficult to understand how the QMC doctors reached that score. For example, setting aside the evidence that the patient took Oxy-Cleanse rather than OxyElite Pro, Patient 7 discontinued dietary supplement use two weeks before ALT was assessed. The patient received NAC, which helps improve liver values, precluding an assessment of the natural ALT course. The score should more likely have been zero for this item, which would mean that the RUCAM score for this patient should have been no more than +4 (and not the +7 reported). In addition, other possible causes of the liver illness were not excluded, so the RUCAM score should have been even lower.

Johnston (2015) presents this death case as one of two "illustrative cases" that they discuss in some detail. The authors give the same RUCAM score that the QMC doctors gave in the Roytman Letter -- +7. According to Johnston (2015), use of OxyElite Pro ceased on September 7 but laboratory values were not taken until September 22, 2013. As noted above, a two-week gap means that the RUCAM item score for cessation of use should be 0 and not +3. This fact alone calls into question the assessment in Johnston (2015).

The Johnston (2015) article states that this patient's "work-up was negative for alternative etiologies,"[215] but does not mention that common causes of liver failure were not in fact excluded. Although Johnston (2015) says nothing about Wilson's disease, the MMWR abbreviated report published in 2013 by many of the same authors claimed that Wilson's

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[212] Patient 7, Production (QMC 000698).

[213] Patient 7, Production (QMC 000297).

[214] Patient 7, Production (Oct. 3, 2013) (QMC 000600).

[215] Johnston, *supra* note 138.

disease and other common etiologies were excluded for all the patients.[216] Johnston (2015) stated that these tests were done only "at the discretion of the diagnosing physician."[217] In any event, the documents we reviewed do not show a single case where the QMC doctors excluded Wilson's disease.

V. Opinions of Scientific Experts

In the course of ongoing civil litigation in Hawaii, several scientific experts for the defendants have opined that OxyElite Pro did not cause the liver illnesses of the Hawaii patients. These opinions, summarized below and attached to this letter (collectively, as Appendix 3), also provide strong reasons to conclude that OxyElite Pro did not cause liver injury in Hawaii.

A. Robert G. Gish, M.D. -- Hepatology/Gastroenterology[218]

Dr. Robert G. Gish is Professor of Clinical Medicine at Stanford and UNLV. Trained in toxicology, he has an M.D. from the University of Kansas, and he completed a fellowship in gastroenterology and hepatology at UCLA in 1988.

Is his expert report, Dr. Gish opined that OxyElite Pro did not contribute substantially to the liver injury of the Hawaii cases. First, he concluded that OxyElite Pro with aegeline is not hepatotoxic. Scientific literature indicates that aegeline is not hepatotoxic, with much evidence for its safety and no peer-reviewed studies to the contrary. Various forms of liver injury can mimic drug-induced liver injury, and the liver biopsy slides Dr. Gish reviewed were non-specific and consistent with multiple etiologies. Most of the biopsy specimens also showed extensive destruction of liver tissue, making it impossible to establish causation.

Second, alternative etiologies or other factors explain the alleged cluster. Alternative etiologies include autoimmune hepatitis, viruses, systemic infection, and environmental toxins. Noting more than a dozen viral serologies that the QMC doctors should have examined, he stated that there was an incomplete workup of the Hawaii patients. One of the more notable overlooked tests was the HEV PCR assay, which was not conducted for any patients. Dr. Gish also offered opinions as to potential alternative etiologies specific to several Hawaii patients who filled lawsuits against OxyElite Pro (e.g., Patients 1-4, 7). His conclusions for these patients are similar to the conclusions made in articles published by Teschke and his colleagues.[219] Dr. Gish

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[216] Park et al., *supra* note 3 ("Excluded were other etiologies such as pre-existing autoimmune hepatitis, chronic alcohol use, and chronic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, and hemochromatosis.").

[217] Johnston, *supra* note 138.

[218] *See* Expert Report of Robert G. Gish, M.D. (Sept. 22, 2015).

[219] Teschke & Eickhoff (2016), *supra* note 11; Teschke et al. (2016), *supra* note 11; Teschke et al. (2015), *supra* note 11.

opined that viral or environmental toxins were the most probable causative agent for many of the patients, especially hepatitis E. Dr. Gish noted also that N-acetylcysteine should be administered immediately anytime a patient is diagnosed with acute liver failure, regardless of the cause, yet the QMC doctors did not do this for any patient whose records he reviewed.

Dr. Gish discussed the RUCAM scale and its limitations. He opined that the scores attributed to the patients in the Roytman Letter to the Editor were based on an incomplete analysis. Noting Dr. Teschke's corrected score of "1" for Patient 8, which the QMC doctors incorrectly scored as a "10," Dr. Gish stated that the QMC's scores must be re-evaluated.

B. Robert D. Gibbons, Ph.D. -- Statistics[220]

Dr. Robert D. Gibbons is a Professor of Public Health Sciences, Medicine, and Psychiatry, and the Director of the Center for Health Statistics at the University of Chicago. He has also served on the Institute of Medicine (IOM) Committee on Drug Safety. He received his PhD in Statistics and Psychometrics from the University of Chicago in 1981.

Using MarketScan Commercial and Medicaid data for patients ages 16-66 (the age range of cases identified by regulators), Dr. Gibbons analyzed reported liver illnesses in the period before and after OxyElite Pro containing aegeline was released into the market. Dr. Gibbons defined the period after introduction of aegeline (which he deemed the "post-Aegeline" period) as November 2012 through August 2013. He used August 2013 as the end to preclude any stimulated reporting that occurred after the story was reported in the media in September 2013. Dr. Gibbons also looked at sales data for OxyElite Pro.

Based on these data, Dr. Gibbons concluded:

(1) If aegeline-containing OxyElite Pro caused the alleged outbreak, there would have been an additional 2,133 cases in the U.S. the following year. In fact, there were 1,294 fewer cases among people with private insurance and Medicaid

(2) The rates of acute hepatitis and liver failure significantly decreased among people with private insurance following the introduction of aegeline-containing OxyElite Pro, and remained unchanged for people on Medicaid.

(3) At the state level, there was no association between OxyElite Pro per capita sales and the rate of acute hepatitis and liver failure.

(4) To a reasonable degree of scientific certainty, the Hawaii "outbreak" was not due to the inclusion of aegeline in OxyElite Pro.

Dr. Gibbons also offered numerous criticisms of the Klontz article,[221] is also discussed above in Section IV.A of this letter:

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[220] *See* Expert Report of Robert D. Gibbons, Ph.D. (Sept. 29, 2015).

- The Klontz article is a retrospective observational trial with no controls.
- Klontz did not even not attempt to adjust the raw number of adverse events for the population at risk.[222]
- Klontz relied on data from the Hawaii DOH (which was received from the QMC doctors) as well as MedWatch reports. MedWatch reports are inherently unreliable. For example, MedWatch reports fail to account for other drugs the patient is taking. In addition, the Klontz paper contains a number of factual inaccuracies.
- Klontz reported that aegeline-containing OxyElite Pro was introduced in April 2013, when it was actually introduced in November 2012. The date is important because no relevant adverse events predate May 2013.
- The vast majority of the reports cited by Klontz were submitted after the media reported the story in September 2013, suggesting the Klontz paper's results were an artifact of stimulated reporting.
- The Klontz paper suggests there was a national increase in liver disease starting in the summer of 2013, but it provides no data or references as to the basis for that assertion.
- The Klontz paper was based on the period from February 2012 to February 2014, which includes reports both before and after OxyElite Pro with aegeline was on the market.
- Of the 55 adverse events related to the liver injury over two years, 36 were from Hawaii for only a 7-month time period. This overrepresentation of Hawaii calls into question whether the cases identified in the Klontz paper are reliable and representative.

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[221] Klontz et al., *supra* note 131.

[222] Dr. Gibbons wrote: "We do not know the number of people who took the drug or supplement and did not experience the adverse event and we do not know the frequency with which people who did not take the drug or supplement experienced the adverse event. Indeed, a drug or supplement can have spontaneous reports of an adverse event and actually be protective (i.e., reduce risk) if the base-rate of the adverse event in patients with the same condition who did not take the drug or supplement is higher than for those who took the drug or supplement. . . . no attempt at all is made to even adjust the raw number of adverse events for the population at risk . . . in the case of the Klontz paper."

C. M. Eric Gershwin, M.D. -- Liver Immunology[223]

Dr. Eric Gershwin is Distinguished Professor of Medicine and Chief of the Division of Rheumatology, Allergy and Clinical Immunology at the University of California at Davis School of Medicine. He has been a consultant to the Office of Dietary Supplements at the NIH, as well as to FDA, FTC, USDA, and DOJ. He received his M.D. from Stanford University in 1971 and his B.A. in zoology and mathematics from Syracuse University in 1966.

In his expert report, Dr. Gershwin included four points about the biochemistry of OxyElite Pro:

(1) The components are water-soluble, and there is no evidence they accumulate in the body.

(2) They are all naturally occurring products.

(3) There is no evidence any of the ingredients elicit an immunological response towards the liver.

(4) There is no clinical data of drug interactions with the components of OxyElite Pro.

Referring to the Hawaii patients, he pointed out that several worsened after discontinuing use of OxyElite Pro, which is inconsistent with both drug-induced hepatitis and other forms of drug-induced autoimmunity. Dr. Gershwin criticized the regulators' investigation of the Hawaii cases because the regulators did not use any case controls and because the investigation was tainted by selection bias (individuals being chosen over others for the report), exclusion bias (exclusion of other patients who had acute liver failure but did not take OxyElite Pro), and observer bias (doctors continuing to use the same diagnosis originally proposed without independent evaluation of how the data was obtained). He stated that such biases lead to overestimation of the data and incorrect interpretations.

Dr. Gershwin then walked through numerous studies of *Aegle marmelos* (the Bael fruit that contains aegeline as a constituent) and its extracts, finding no evidence of toxicity in those studies. He cited recent literature suggesting *A. marmelos* may have hepatoprotective qualities.

Dr. Gershwin concluded that there is no medical, experimental, or animal data to support the conclusion that consumption of OxyElite Pro was associated either directly or indirectly with liver failure.

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[223] *See* Expert Report of M. Eric Gershwin, M.D. (Sept. 30, 2015).

D. Christopher Borgert, Ph.D. -- Pharmacology/Toxicology[224]

Dr. Christopher Borgert is President and Principal Scientist at Applied Pharmacology and Toxicology, Inc. He also works at the University of Florida, College of Veterinary Medicine's Department of Physiological Sciences. He received a Ph.D. in Pharmacology from the University of Florida in 1991.

In his report, Dr. Borgert noted the lack of scientific literature demonstrating that aegeline causes liver injury. He also discussed the challenges in assessing idiosyncratic liver injury. Such injuries are neither predictable nor reproducible because they are dependent on host factors rather than pharmacodynamics and pharmacokinetics. Thus, idiosyncratic liver injury is extremely difficult, if not impossible, to identify. He noted that, given the fact that OxyElite Pro was used nationally, the clustering of the cases should have led to the conclusion that OxyElite Pro was an unlikely cause.

Dr. Borgert also analyzed the QMC doctors' claim that aegeline is structurally similar to MDMA and amphetamine. He noted that aegeline is structurally similar to dozens of compounds, not merely MDMA and amphetamine, and that these dozens of compounds have markedly different effects. Structural similarity, he stated, is a poor basis for predicting many properties, including hepatotoxic properties. In addition, there are no published reports indicating that aegeline has effects similar to MDMA or amphetamine.

Dr. Borgert concluded that aegeline-containing products do not cause or contribute to liver failure.

E. Hartmut Jaeschke, Ph.D., ATS -- Toxicology/Biochemistry[225]

Dr. Harmut Jaeschke is Chairman and a Professor in the Department of Pharmacology, Toxicology and Therapeutics at the University of Kansas College of Medicine. He received his Ph.D. in toxicology in 1983 his M.S. in biochemistry in 1981 from the University of Tubingen in Germany. Dr. Jaeschke has served as a principal investigator in studies funded by the NIH regarding drug hepatotoxicity.

In his report, Dr. Jaeschke stated that the scientific literature contains no information to suggest toxicity of aegeline or extracts of the Bael tree (*A. marmelos*). In fact, he noted some reports show that Bael extracts promote health. Dr. Jaeschke also reviewed five preclinical studies in animal species and one limited human study, noting that none found adverse effects of any kind. He stated that the exposure in the animal studies ranged from 176-352 times the exposure of the Hawaii cases, and the cumulative exposure in one of the studies was over 1,000 times.

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[224] *See* Expert Report of Christopher Borgert, Ph.D. (Sept. 30, 2015).

[225] *See* Expert Report of Hartmut Jaeschke, Ph.D., ATS (Sept. 30, 2015).

Dr. Jaeschke concluded that the ingredients in OxyElite Pro, and particularly aegeline, do not have a potential for hepatotoxic effects.

F. Noel S. Weiss, M.D., Dr.PH -- Epidemiology[226]

Dr. Noel S. Weiss is a Professor in the Department of Epidemiology at the University of Washington's School of Public Health and Community Medicine (1979-present). He received a DrPH in Epidemiology and Biostatistics in 1971 and an MPH in 1969 from Harvard School of Public Health. He received his M.D. in 1967 and B.A. in 1965 from Stanford University.

In his report, Dr. Weiss criticized the methodology employed by the QMC doctors and the regulators. The Roytman Letter to the Editor described a mere case series, not a case-controlled study. Similarly, the regulators conducted an "investigation to describe case patients," which was unable to examine the potential role of OxyElite Pro, or any other drug or dietary supplement, as a factor in the development of acute hepatitis and liver failure. Dr. Weiss concluded that the regulators' approach "did not have the potential to elucidate etiologic factors."

G. Joseph V. Rodricks, Ph.D., DABT -- Toxicology/Human Health Risk Assessment[227]

Dr. Joseph V. Rodricks is co-founder and Principal at Ramboll Environ US Corporation, and an internationally recognized expert in toxicology and risk analysis. He is also a Visiting Professor in toxicology and risk assessment at the Johns Hopkins Bloomberg School of Public Health. Dr. Rodricks is a former Associate Commissioner at FDA. He received his Ph.D. in biochemistry from the University of Maryland in 1968 and was a post-doctoral scholar at the Department of Biochemistry at the University of California at Berkeley from 1969-1970. He received a B.S. in chemistry from the Massachusetts Institute of Technology in 1960.

In his report, Dr. Rodricks analyzed the available data on the safety of aegeline. He first evaluated the clinical data -- the USPlabs in-house pilot study -- and found no indication of aegeline-related adverse effects on liver function. He then evaluated the various animal studies that found no adverse effects or other signs of toxicity. These studies include multi-dose testing indicating no adverse effects at human equivalent doses up to 48 times higher than the maximum recommended intake of OxyElite Pro. Dr. Rodricks also cited the historical use of aegeline-containing extracts of *A. marmelos* in foods and traditional medicine treatments, which further supports the safety of aegeline.

Dr. Rodricks concluded that the available information on the toxicity of aegeline from studies in humans and animals gives no indication that aegeline is capable of causing liver

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[226] *See* Expert Report of Noel S. Weiss, M.D., Dr. PH (Sept. 22, 2015).

[227] *See* Expert Report of Joseph V. Rodricks, Ph.D., DABT (Sept. 30, 2015).

damage, and that there is no adequate data to conclude that OxyElite Pro was responsible for the liver injuries allegedly sustained by the Hawaii cases.

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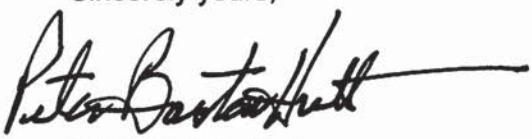
Three other experts for the defendants filed reports related to damage calculations. These are not attached because they are not relevant to OxyElite Pro.

VI. Conclusions

The patient records and deposition testimony of the QMC doctors do not support their statements to the media and in publications concerning the causality between OxyElite Pro and liver disease. As a result of their actions, both regulators and the patients themselves have received and relied upon erroneous information. At the same time, Dr. Wong testified that QMC's business increased,[228] and they succeeded in bringing national attention to their liver center.

We request that the FDA record with respect to the OxyElite Pro recall be reopened to include this letter. Please let us know if you have any questions about any of the statements made in this letter.

Sincerely yours,



Peter Barton Hutt

Matthew Jon Hegreness

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[228] Wong Deposition, 123:15-19 ("Q. So it's fair to say this cluster generated more business for you? A. Yes.").

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